PATTERN OF RESPONSE TO FECAL MICROBIOTA TRANSPLANTATION IN PATIENTS WITH ACTIVE ULCERATIVE COLITIS

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By

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Dedicated to my Teachers, Family and Friends

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Dr. Halgale Tanveer Jakirhusain...

ABBREVATIONS

1.	UC	-	Ulcerative Colitis
2.	IBD	-	Inflammatory Bowel Disease
3.	FMT	-	Fecal microbiota transplantation
4.	CDI	-	*Clostridium difficile* infection
5.	GI	-	Gastrointestinal
6.	TLR	-	Toll like receptors
7.	NF-Kb	-	nuclear factor kappa light chain enhancer of activated B cells
8.	TNF-α	-	Tumour Necrois Factor- α
9.	Th2	-	Helper T cells type 2
10.	CXCL	-	Chemokine (C-X-C motif) ligand
11.	rCDI	-	Recurrent *Clostridium difficile* infection
12.	Treg	-	T- Regulatory
13.	IL	-	Interleukin
14.	RCT	-	Randomized control trials
15.	SOC	-	Standard of care
16.	FDA	-	Food and Drug Administration
17.	E.coli	-	Escherichia Coli*
18.	5-ASA	-	5-Amino Salicylic Acid
19.	SCCAI	-	Simple Clinical Colitis Activity Index
20.	HIV	-	Human Immunodeficiency Virus

21.	HCV	-	Hepatitis C Virus
22.	HBsAg	-	Hepatitis B Surface Antigen
23.	BMI	-	Body Mass Index
24.	SPSS	-	Statistical Package for the Social Sciences
25.	NO.	-	Number
26.	Std	-	Standard
27.	M:F	-	Male: Female
28.	AZT	-	Azathioprine
29.	ER	-	Endoscopic Remission
30.	CD	-	Crohn’s Disease

KEY TO MASTER CHART

1.	S.no	-	Serial Number
2.	M	-	Male
3.	F	-	Female
4.	AZT	-	Azathioprine
5.	N	-	No
6.	Y	-	Yes
7.	BMI	-	Body mass Index
8.	hsCRP	-	High sensitivity C- Reactive protein
9.	E	-	Extent of disease
10.	ER	-	Endoscopic Remission
11.	UCEIS	-	Ulcerative Colitis endoscopic index of severity
12.	SCCAI	-	Simple Clinical Colitis Activity Index

ABSTRACT

Introduction: Faecal microbiota transplantation (FMT) as a potential treatment for inflammatory bowel disease (IBD) is an area of active current research. Faecal microbiota transplantation (FMT) is the artificial replacement of a 'dysbiotic' microbiota with one from a healthy individual.However there is paucity of data which looks into the pattern of response to FMT, its optimal timing and optimal dosing frequency

Aim of Study: To study the Pattern of response of FMT in patients with Active Ulcerative Colitis.

Materials & methods: This is an interventional, prospective and uncontrolled study. Patients with Active Ulcerative Colitis based on Mayo Clinic score $\geq$ 3 are included. Patients are continued on their standard of care treatment and FMTs are done at week 0, 2, 6, 10, 14, 18 and 22 weeks. Response at each visit is assessed using Mayo Score and SCCAI. Primary outcome is to determine the number of FMT sessions needed to achieve Clinical remission.

Results: Thirty-three patients were enrolled during the study period. Six patients were lost to follow up over the duration of the protocol. The mean age of patients was 31.12 years. The mean retention time progressively improved over successive visits (Mean retention time 2.54 $\pm$ 1.35 hours at visit 1 to 4.81 $\pm$ 0.73 hours at the 7^{th} visit). Clinical Remission and Endoscopic remission was achieved in 77.8% and 81.5% respectively at the 7^{th} visit. The mean Total Mayo score and mean SCCAI improved over the subsequent FMT sessions, trend analysis suggested a significant downward trend with a Kendall Coefficient of 0.707 and 0.716 respectively with a p value of <0.01 for both. Post Hoc analysis and the Kendall Coefficient scores at different visits suggested that the benefit in the total Mayo score after the 4^{th}visit was not statistically significant.

Conclusion: Intensive multisession FMT has demonstrated a significant reduction in the disease activity with a relative plateauing of the benefit after the 4^{th} session of FMT. The procedure was relatively safe with no serious adverse events. Further research is required to delineate the exact protocol with respect to the number of FMT sessions and patient and donor selection.

Keywords: Faecal Microbiota Transplantation, Ulcerative Colitis, Dysbiosis, Mayo score

TABLE OF CONTENTS

S. NO.	TOPIC	PAGES
I	INTRODUCTION	1-2
II	AIMS AND OBJECTIVES	3
III	REVIEW OF LITERATURE	4-15
IV	MATERIALS AND METHODS	16-23
V	OBSERVATIONS AND RESULTS	24-53
VI	DISCUSSION	54-59
VII	SUMMARY AND CONCLUSIONS	60-61
VIII	BIBLIOGRAPHY APPENDICES – I - PROFORMA - MASTERCHART	62-68
	APPENDICES – II - APPROVAL LETTER OF THESIS PLAN - THESIS PLAN	

LIST OF TABLES

Table No.	Title	Page No.
1	Montreal Classification for Extent of Ulcerative Colitis	16
2	Mayo Score	18
3	Simple Clinical Colitis Activity Index (SCCAI)	19
4A	Age Distribution	24
4B	Age Distribution	26
5	Gender Distribution	26
6A	Disease Duration	27
6B	Disease Duration	28
7A	BMI	28
7B	BMI	28
8	Comorbidities	29
9A	Previous Exposure To Biologicals And Immunomodulators	30
9B	Concurrent Immunomodulators	30
10A	Exposure to oral steroids	32
10B	Exposure to I.V. steroids	32
11	Retention Time	33
12	Mayo Score--Number Of Stools	34
13	Mayo Score-Blood In Stools	35
14A	Endoscopic Mayo Score	36

14B	Comparison of association of Endoscopic Mayo Score Over Time Tends using Mann Kendall test	37
15	Disease Severity At Baseline	37
16A	Total Mayo Score	39
16B	Comparison of association of Mayo Score Over Time Tends using Mann Kendall test	40
16C	Comparison of the Kendall coefficient coefficient of concordance at different visits	40
16D	Post Hoc Analysis Of The Mean Mayo Score Trend	41
17	Clinical Remission	42
18	Endoscopic Remission	44
19	Clinical Response	46
20A	Simple Clinical Colitis Activity Index	47
20B	Proportion of patients with SCCAI $\leq$ 1	48
20C	Comparison of association of SCCAI Score Over Time Tends using Mann Kendall test	50
21	Extent of Disease	51
22	Adverse Effects	53

LIST OF FIGURES

Figure No.	Title	Page No.
1	Bristol Stool Chart	21
2	Age Distribution	25
3	Gender Distribution	26
4	Disease duration in years	27
5	Comorbidities	29
6	Concurrent Immunomodulators	31
7	Exposure to Steroids	32
8	Retention Time	33
9	Mayo Score--Number Of Stools	34
10	Mayo Score-Blood In Stools	35
11	Endoscopic Mayo Score	36
12	Disease severity at Baseline	38
13	Mean Mayo score	39
14	Proportion of patients with clinical Remisson at each visit	43
15	Proportion of patients with Endoscopic Remission	45
16A	Simple Clinical Colitis Activity Index	47
16B	Proportion of patients with SCCAI $\leq$ 1 at every visit	49
17	Extent Of Disease	52

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by colonic mucosal inflammation occurring at the interface between the luminal contents and the mucosal immune system. The precise etiology of UC is unclear, with interaction of genetic, environmental, and microbiological factors likely playing a role[1]. Although the precise cause of IBD remains unknown, the most accepted hypothesis of IBD pathogenesis to date is that an aberrant immune response against the gut microbiota is triggered by environmental factors in a genetically susceptible host[2]. The prevalence of IBD is greatest in the developed world affecting one million people in USA, 2.5 million in Europe and the prevalence is increasing in developing countries. Recent studies from China, India and Middle East reported prevalence of between 2.0 and 6.0 per 100,000 individuals[3].

The human gut contains, in the assortment of 1000 bacterial species, 100-fold more genes than the human genome. More than 90 % of the human gut microbiota is composed of four major phyla. The Firmicutes (49–76 %) and Bacteroidetes (16–23 %) phyla dominate, followed to a much less extent by the Proteobacteria and Actinobacteria phyla[4]. Most studies have shown reduced diversity of the gut microbiota in IBD patients. The most consistent observations of altered composition of the gut microbiota in IBD patients are a reduction in Firmicutes and an increase in Proteobacteria[2]. Although these changes in the gut microbiome may be a result of increased inflammation, evidence suggests that it is more likely that the alteration in microbiota are involved in pathogenesis, either due to intolerance to a specific group of commensals or due to an imbalance between the protective and harmful members of the population[5].

Fecal microbiota transplantation (FMT) is a technique in which intestinal microbiota are transferred from a healthy donor to the patient, with the goal of introducing or restoring a stable microbial community in the gut. FMT might have augmented capacity to correct the complex

microbial disturbances associated with ulcerative colitis[6]. Fecal microbiota transplantation has long been used to treat recurrent Clostridium difficile infection (CDI) presenting great effectiveness and significant safeness, with cure rates reaching 90%(7).

Current medical treatment of IBD remains imperfect. There have been advances in the medical therapy, but these have not translated into appreciable clinical success. Moreover the focus of drug development has been on altering the immune response rather than targeting the factors which lead to activation of the abnormal immune response. FMT has emerged as a novel approach which targets the pathophysiology of IBD i.e. alteration in gut microbiome. Several studies have evaluated the role of FMT in Ulcerative colitis with studies utilizing different protocols and FMT schedules which report beneficial effect of FMT in induction and maintenance of remission in patients with active Ulcerative Colitis. This study intends to assess the pattern of response to multiple cycles of FMT in patients with Active Ulcerative Colitis.

AIMS AND OBJECTIVES

- To study the pattern of response to fecal microbiota transplantation in patients with active ulcerative colitis

REVIEW OF LITERATURE

Ulcerative colitis (UC) is a relapsing remitting disorder characterized by inflammation limited to mucosal surface of the large bowel. The disease starts in the rectum and in most cases extends proximally in a continuous fashion. The absence of rectal involvement has been noted in fewer than 5% of adult patients with UC at diagnosis but may be seen in up to one-third of pediatric-onset colitis[8].

EPIDEMIOLOGY

The annual incidence of ulcerative colitis varies from 0–19.2 per 100,000 in North America and 0.6–24.3 per 100,000 in Europe[9]. Inflammatory bowel disease (IBD), once considered to be a Western disease, is increasingly being reported from India and other Asian countries. These obvious inconsistencies in disease distribution have been attributed possibly due to artefacts of methodology, genetic and environmental factors, or even subtler sociological variables such as stigma and underreporting. However, recent epidemiological experience is changing these premises. The disease is beginning to make itself known in populations where it had never been seen before, such as the Chinese in Hong Kong, the Chinese in Singapore, and the Arabs in Kuwait[10]. An increased incidence is also being reported from the previously low incidence areas of Australia and Eastern Europe[11].

The Indian disease pattern is going through a phase of epidemiological transition with a surge in the incidence of IBD. There are two studies, both from northern states, which have reported the population prevalence of UC. In a house to house survey of 21,971 persons in Haryana in 1984, a prevalence rate of 42.8 per 100,000 population was recorded[12]. The second study, conducted in Ludhiana, Punjab, screened a population of 51,910 through a cluster random sampling method establishing a crude prevalence rate of 44.3 per 100,000 population. The crude incidence rate calculated after a second visit 1 year later was estimated to be 6.02 per 100,000 population[13]. In a

recent epidemiological study from 13 countries in Asia, India was found to have the highest incidence rate of IBD at 9.31/100,000[14].

MICROBIOME:

The human gastrointestinal (GI) tract represents one of the largest interfaces (250–400 m^2) between the host, environmental factors and antigens in the human body. The collection of bacteria, archaea and eukarya colonising the GI tract is termed the 'gut microbiota' and has co-evolved with the host over thousands of years to form a complex and mutually beneficial relationship[15]. The number of microorganisms inhabiting the GI tract has been estimated to exceed 10^{14}, which incorporates ~10 times more bacterial cells than the number of human cells and approximately 100 times the amount of genomic content as the human genome[16].The microbiota offers many benefits to the host, through a range of physiological functions such as strengthening gut integrity, protecting against pathogens and regulating host immunity[17].

Studies have identified 2172 species in the human-associated microbial repertoire which are further classified into 12 different phyla, of which 93.5% belonged to Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes[18]. According to aerobiosis or anaerobiosis, the intestinal microorganisms are divided into anaerobic bacteria, facultative anaerobic bacteria, and aerobic bacteria; anaerobic bacteria are the most abundant intestinal bacteria[19]. These bacteria are mainly distributed in the colon and distal small intestine. Most of the bacteria live on the surface of the intestinal mucosa. They attach to the surface of the intestinal epithelial cells to form a layer of bacterial biofilm, which ultimately affects the intestinal metabolism of nutrients, intestinal permeability, and intestinal immune system function.

According to their role in the host, intestinal microbiota can be divided into three categories. The first category contains the physiologic bacteria that are in a symbiotic relationship with the host. They attach to the deep mucosal epithelial cells and are mostly anaerobic. They are the principal microbiota of the intestine (e.g., Bifidobacterium, Bacteroides, and Peptococcus) and play major roles in nutrition and

immune regulation. They help inhibit intestinal colonization by pathogens, occupy the intestine and prevent pathogens from invading the lamina propria layer. They also contribute to the formation and improvement of the intestinal immune system, which monitors and removes harmful bacteria to maintain the body health. The second category contains conditional pathogens that inhabit the host. They are mainly facultative aerobic bacteria and intestinal nondominant bacteria (e.g., Enterococcus and Enterobacter). These organisms are not dangerous when intestinal microecological balance is maintained but can be harmful to humans under certain conditions. The third category contains mostly pathogenic bacteria (e.g., Proteus and Pseudomonas). When microecology is in balance, long-term colonization of pathogens is rare, and the number of these organisms is small and nonpathogenic. If changes in the enteral and external environments lead to a decline of intestinal-dominant microbiota, then dysbiosis will occur, with pathogens or conditional pathogens increasing to the point of causing disease[20].

PATHOPHYSIOLOGY OF ULCERATIVE COLITIS:

Pathophysiology of UC is complex. The epithelial barrier, covered by a mucinous layer, is the first-line defence of the mucosal immune system, because it provides physical separation between host immune cells and luminal microbes, and synthesises antimicrobial peptides. Damage to the epithelial barrier leads to increased permeability, possibly due to defective regulation of tight junctions[21]. This barrier loss enables increased uptake of luminal antigens. Antigens activate the innate immune response through interaction with macrophages and dendritic cells. Macrophages and dendritic cells (innate immune cells), on recognition of bacteria through molecular pattern recognition receptors (TLR), change their functional status from tolerogenic to an activated phenotype. Activation of NF-kB pathways stimulates the transcription of proinflammatory genes, resulting in increased production of proinflammatory cytokines namely TNF-α, interleukins 12, 23, 6, and 1β. After processing of antigens, macrophages and dendritic

cells present them to naive CD4 T-cells, promoting differentiation into Th2 effector cells, characterised by production of interleukin 4. In the mucosa of patients with ulcerative colitis, the homoeostatic balance between regulatory and effector T-cells (e.g., T-helper [Th] 1, Th2, and Th17) is disturbed. Ulcerative colitis is associated with an atypical Th2 response mediated by non-classic natural killer T-cells producing interleukins 5 and 13. Interleukin 13 is of particular importance because it exerts cytotoxic functions against epithelial cells, including induction of apoptosis and alteration of the protein composition of tight-junctions[22]. Circulating T cells bearing integrin-α4β7 bind to colonic endothelial cells of the microvasculature through the mucosal vascular addressin-cell adhesion molecule -1, whose expression is enhanced in the inflamed intestine, leading to increased entry of gut-specific T cells into the lamina propria. Upregulation of inflammatory chemokines, such CXCL1, CXCL3, and CXCL8, leads to recruitment of circulating leucocytes which perpetuates the cycle of inflammation[23].

MICROBIOTA AND ULCERATIVE COLITIS:

Mucosal immune system has two important functions. It needs to be tolerant of the overlying microbiota to prevent the induction of an excessive and detrimental systemic immune response and it needs to be able to control the gut microbiota to prevent its overgrowth and translocation to systemic sites. Tolerance at the GI mucosa is interplay of three moieties: modification of the antigenic moieties of the microbiota, modulation of the host response and physical separation of the bacteria and the host cells. Gut microbiota provides physical barrier to incoming pathogens by competitive exclusion, occupation of attachment sites, consumption of nutrient sources and production of antimicrobial substances.

When the balance of intestinal microbiota is broken, the intestinal defence function and immunoregulatory function are decreased, the immunity of the body is reduced, and the relative pathogenic factors are increased so as to cause the intestinal mucosal invasion or aggravate the diseases. Under normal circumstances, the host's innate

and adaptive immunity prevents the invasion of harmful bacteria while tolerating the normal microbiota. However, if the microbiota is imbalanced, immunity is compromised. The intestinal mucosal immune response is overstimulated, which can lead to disease[24].Rapid rise in pathogenic bacteria and enterotoxin release increases intestinal mucosal permeability, and causes immune dysfunction. Excessive growth of some bacteria affects metabolic and energy metabolism, triggering intestinal inflammation and damage of the intestinal mucosa[20].

FECAL MICROBIOTA TRANSPLANTATION:

Fecal microbiota transplantation (FMT) is the administration of a solution of fecal matter from a donor into the intestinal tract of a recipient in order to directly change the recipient's microbial composition and confer a health benefit. The first known description of the use of faeces as therapy was described by Ge Hong in fourth-century China as fresh or fermented faecal products, called "yellow soup", to treat severe diarrhoea, fever, pain and constipation. There are also descriptions during the sixteenth century Ming dynasty whereby patients were prescribed fresh or fermented fecal suspensions for a range of GI conditions, including diarrhea, vomiting, constipation, and pain[25]. Subsequent accounts refer to Fabricius Aquapendente, an Italian seventeenth century anatomist who used FMT in veterinary medicine. It was termed "transfaunation"[26].

In 1958, Eiseman and colleagues described the use of fecal enemas as a treatment for pseudomembranous colitis, marking the introduction of FMT into mainstream medicine[27]. First report of the use of FMT to treat CDI came in 1983. The greatest evidence for FMT is for treatment of recurrent CDI. The first randomized controlled trial for FMT in this setting was reported in 2013 in which FMT was performed through the nasoduodenal route[28]. There have been 2 randomized controlled trials showing efficacy of FMT via colonoscopy[29, 30]. Among most studies for CDI, the highest cure rates are seen with colonoscopic administration of donor stool, generally greater than 90%. Oral administration is

slightly less effective with resolution rates in the 76% to 79% range[31]. For recurrent CDI, Konijeti and colleagues performed decision analysis to ascertain if FMT was a cost-effective strategy. Comparing various treatment strategies, FMT via colonoscopy was the most cost-effective initial strategy for rCDI[32]. Encouraged by the success of FMT in C. difficile, there has been considerable interest for the role of FMT in IBD. There have been multiple case reports and series describing differing FMT protocols, methods of stool administration, and variable patient responses, however there is no fixed protocol for the route or method of administration.

FECAL MICROBIOTA TRANSPLANTATION IN ULCERATIVE COLITIS:

The success of FMT for C. difficile infections has encouraged research examining it as a potential therapy for other diseases possibly influenced by the microbiome such as IBD. FMT is proposed to treat UC by modifying the colonic ecosystem, but the potential biochemical and/or immune mechanisms by which this may occur are unknown.

Gut microbiome within an individual is variable and dynamic and therefore defining a “normal” healthy gut microbiome is not possible at the moment. As discussed earlier, the health of the microbiome depends upon its barrier function to incoming pathogens by competitive exclusion, its resistance to disruptions and its ability to revert to its baseline composition even if disturbed. If the effects induced by external factors exceed the ability of microbial community to resist the change, resulting dysbiosis can affect the functionality of the intestinal microenvironment culminating in unfavourable consequences[33]. As discussed, the exact cause of the immune response in IBD is still obscure. Further, whether dysbiosis is a cause or an effect of altered immune and metabolic environment of the inflamed mucosa is unclear. Dysbiosis in IBD is characterized by reduction in Bacteroidetes, reduced diversity within Firmicutes and an increased proportion of Proteobacteria[34]. FMT is expected to correct this dysbiosis and thereby reduce gut inflammation in UC. However, to date, no specific

group of microbes have been established in relation to response to FMT in UC.

Commensal microorganisms play an important role in development as well as maturation of the mucosal immunity, synergistically cooperate in nutrient digestion and metabolism and intensely compete for nutrients and space. Dysbiosis in IBD dysregulates gut homeostasis as well as hampers several immune mechanisms that work in tandem with the microbiota for the maintenance of the same. FMT is postulated to re-establish this equilibrium by correcting dysbiosis.

Animal models have shown reduced colonic inflammation following FMT due to reestablishment of colonic CD4+ and Treg cells, increase in interleukin-10 (IL-10) production, reduced ability of antigen presenting cells to present bacterial antigens to the colonic T cells, and restoration of intestinal memory/effector T cell populations[35]. The current understanding of immunoregulatory changes with FMT is limited and well-designed focused studies with adequate sample sizes are needed.

The application of FMT in UC was first published as a case report by Justin Bennet in 1989 when he treated his own refractory UC after administration of donor microbiota via fecal enemas and achieved both clinical and histological remission without any additional medications[36]. In 2012 Angelberger et al. reported their results of FMT used to treat five patients with immunotherapy-refractory UC. Only one patient responded following 3 days treatment using FMT by a combined nasojejunal plus enema-delivered approach and this patient"s microbiota resembled that of the donor[37]. In 2013, a study was conducted in patients aged 7-21 years of age which used freshly prepared faecal enemas for 5 days in treating mild to moderate UC. In this study, seven of the nine subjects showed clinical response within 1 week, six of the nine subjects maintained clinical response at 1 month with a significant reduction in the paediatric UC activity index[38].

Interest in FMT for IBD was amplified after two RCTs evaluating FMT for induction of remission in UC were published with contradictory results in 2015. Moayyedi et al. reported the results of a double blinded randomized placebo-controlled trial using FMT in the form of an enema administered weekly over 7 weeks to patients with active UC. In this study, clinical remission was seen in 9 out of 38 (24%) patients in the FMT arm compared to 2 out of 37 (5%) in the placebo arm. Eight of the nine patients in remission remained in remission after one year. There were no differences in serious adverse events between the FMT and placebo. Stool from patients receiving FMT had greater microbial diversity, compared with baseline, than that of patients given the placebo[39].

Rossen et al. undertook a double blinded RCT using the naso-jejunal route to deliver FMT to patients with mild to moderately active UC. They chose to use patient's own stool as placebo. At 8 weeks, they found remission in 6 of 23 (26%) donor-FMT treated vs. 8 of 25 (32%) autologous FMT treated patients. There was no statistically significant difference in clinical and endoscopic remission between patients with UC who received fecal transplants from healthy donors and those who received their own fecal microbiota[40].

Paramsothy et al conducted a 3-centre double-blind, randomised, placebo-controlled trial of multidonor, intensive-dosing faecal microbiota transplantation in patients with active ulcerative colitis. Patients with active ulcerative colitis (Mayo score 4–10) were randomly allocated in a 1:1 ratio, using a preestablished randomisation list, to either faecal microbiota transplantation or placebo colonoscopic infusion, followed by enemas 5 days per week for 8 weeks. Faecal microbiota transplantation enemas were each derived from between three and seven unrelated donors. The primary outcome of steroid free clinical remission was achieved in 11 (27%) of 41 patients allocated faecal microbiota transplantation versus three (8%) of 40 who were assigned placebo (risk ratio 3·6, 95% CI 1·1–11·9; p=0·021), however endoscopic remission did not differ between the groups. There was no

significant difference in number or type of adverse events between treatment groups. Microbial diversity increased with and persisted after faecal microbiota transplantation. Several bacterial taxa were associated with clinical outcome; in particular, the presence of Fusobacterium spp was associated with lack of remission[41].

In another study from Australia conducted by Costello et al[42], Patients were randomized to receive either anaerobically prepared pooled donor FMT or autologous FMT via colonoscopy followed by 2 enemas over 7 days. They showed that 12/38 (32%) patients achieved steroid-free remission in the pooled donor FMT group compared to 3/35 (9%) patients who received autologous FMT (P = 0.02) in the intention to treat (ITT) analysis. Similarly, clinical response and clinical remission rates were 55% vs. 20% (P < 0.01) and 50% vs. 17% (P < 0.01), respectively. A unique feature of this study was the use of anaerobic stool processing, previous studies having used aerobic stool processing methods. It has been demonstrated previously that many obligate anaerobes, such as Faecalibacterium prausnitzi, are lost with aerobic stool processing but are preserved with anaerobic stool processing[43]. Their stool analysis results showed an increased abundance of Anaerofilum pentosovorans and Bacteroides coprophilus species, and that these species were strongly associated with disease improvement following donor FMT. All the organisms positively associated with the observed treatment response in this study were anaerobes (mostly obligate anaerobes). They suggested that preservation of donor-derived anaerobes may explain the similar clinical effect seen with this low-intensity treatment study when compared with other protocols with more intensive regimes[42].

The possible role of FMT in the maintenance of remission has also been studied. In a recent study conducted by Sood et al, patients with UC in clinical remission after multi-session FMT were randomly allocated to either maintenance FMT or placebo colonoscopic infusion. every 8 weeks, for 48 weeks. The standard of care (SOC) therapy was continued in all patients. The primary end point of steroid free clinical

remission was achieved in 27/31 (87.1%) patients allocated FMT versus 20/30 (66.7%) patients assigned placebo (p=0.111).

Secondary end points of endoscopic remission [FMT: 18/31 (58.1%) versus placebo: 8/30 (26.7%), p=0.026] and histological remission [FMT: 14/31 (45.2%) versus placebo: 5/30 (16.7%), p=0. 033] were achieved in significantly higher number of patients with FMT[44].

In a study from Turkey, researchers studied the efficacy of FMT by assessing the clinical and endoscopic response in patients with ulcerative colitis (UC) who had failed anti-inflammatory and immunosuppressive therapy. They reported that twenty one (70%) of the thirty patients showed clinical response, and thirteen (43.3%) of the thirty patients achieved clinical and endoscopic remission at week 12. Nine patients (30%) were accepted as a non-responder at the end of week 12. No adverse events were observed in the majority of patients during FMT and 12 weeks follow-up[45].

The variability in methodology and conflicting results in the published studies highlight a number of unresolved issues in FMT and the need for further studies that expand on optimal indications, delivery route and frequency, donor selection and need for maintenance therapy. As these RCTs are heterogeneous with regard to the route and dose of administration, number of treatment sessions, choice of placebo, and the exact indication for FMT, the results cannot be compared

UNRESOLVED MATTERS IN THE USE OF FMT FOR ULCERATIVE COLITIS:

Majority of the above discussed studies have middle age patients with mild to moderate disease on stable doses of medications. Additionally, none of the studies have used FMT as the only therapeutic agent or as initial therapy. None of the above published studies have established any concrete interaction between age, sex, disease duration and distribution. The precise group of patients to benefit the most form FMT needs to be delineated.

There is no consensus regarding the route of FMT to be used or the frequency of sessions to be administered. The RCTs with a colonic or rectal instillation of fecal slurry have shown better response rates compared to the upper GI route of administration. In a metaanalysis based on cohort studies, the pooled proportion of clinical remission rates with upper and lower GI tract administration of fecal slurry were 8% and 31%, respectively[46]. A small open label pilot study has demonstrated the efficacy of capsule-based long-term multidonor FMT. However, the number of participants was small and 20% developed serious adverse effects and dropped out[47].

Therapeutic microbial manipulation with a single session of FMT is unlikely to have sustained benefits due to complex and persistent pathologic mechanisms in ulcerative colitis. However, the fixed number of sessions required for the maximal possible benefit and the need for maintenance therapy if any has still not been established. However as quoted above, a study done in India has demonstrated benefit after maintenance therapy in FMT(44). Also the fixed duration of interval between sessions is also not determined with studies employing intervals ranging from 1 -12 weeks[39-42]. In the Indian studies, a colonoscopic route for infusion of FMT was used and the sessions were scheduled at weeks 0, 2, 6, 10, 14, 18, and 22 for induction of remission and subsequently every 8 weeks for maintenance of remission[44,48]. This strategy of multisession FMT may be less demanding in developing countries like India as the cost of colonoscopic FMT is less as compared developed countries.

FMT for patients with UC is still in an experimental stage and is currently not recommended as the standard of care. Its use beyond clinical trials is therefore not recommended. Even for rCDI the FDA exercises its discretion and places it under the ambit of an investigational new drug. The experimental nature of FMT, as well as its potential long-term consequences and the likelihood of achieving therapeutic goals should be discussed with the patient in detail. FMT has the potential for transmitting occult infections even when strict

donor screening is performed. The clinician has to estimate the risk whether the donor had recently contracted a transmissible disease, as well as rule out potential exposure to other pathogenic agents that are not identified by laboratory methods. There have been reports of transmission of drug-resistant E. coli by FMT though in immune-compromised recipients[49].

FMT has caught the imagination of researchers around the world. The science of the gut microbiome is still in its infancy and the clinical use of FMT beyond clinical trials is not recommended at the moment. Also, many issues like patient selection, route and duration of administration, donor selection and continuation of maintenance therapy need to be settled.

MATERIALS AND METHODS

STUDY DESIGN

This study was conducted on the patients attending the outpatient department or admitted in Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, India.

Consecutive patients suffering from active Ulcerative Colitis attending the outpatient or admitted indoors in Department of Gastroenterology, Dayanand Medical College & Hospital were enrolled for the study. Patients providing informed consent were enrolled for the study. Demographics, drug history, comorbidities, disease characteristics like duration, severity (mild, moderate or severe), extent (Montreal classification) and inflammatory markers (hsCRP, when available) were recorded in all patients. Patients were educated about faecal microbiota transplantation (FMT) through a Patient Information Sheet (PIS) which was provided to each patient.

TABLE 1: Montreal Classification For Extent Of Ulcerative Colitis[50]

Extent		Anatomy
E1	Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

Consecutive patients suffering from Active Ulcerative Colitis were enrolled after obtaining informed consent. Donor faeces (200-300 gm) were diluted in 200-300 ml normal saline. After proper blending, the slurry was filtered, and particulate matter removed. The resultant solution was administered to the patient through colonoscopy, within 1 hour of preparation. FMT was completed within 6 hours of passing stools as a fresh sample was used in all patients.

Patients were encouraged to retain the solution for as long as possible. These FMTs were done at weeks 0, 2, 6, 10, 14, 18, and 22 (i.e. seven sessions of FMT).

High fiber diet was advised to stimulate proliferation of infused bacteria. The subjects were continued on their standard of care pharmacological maintenance regimen with dosages of 5-ASA compounds being 3.6gm-4.8gm/day, Azathioprine at 1.5-2 mg/kg/day and steroids were continued in tapering dosages.

SOURCES OF DATA

Consecutive patients suffering from active Ulcerative Colitis attending the outpatient or admitted indoors in Department of Gastroenterology, DMC & H were enrolled for the study.

METHODS OF COLLECTION OF DATA

DATA COLLECTION

Confirmed cases of Active Ulcerative Colitis, defined as having a Mayo score of $\geq$ 3, were enrolled and received FMT for 6 months (at weeks 0, 2, 6, 10, 14, 18, and 22). Disease assessment was done at each visit along the lines of the Mayo Score – Number of stools, blood in stools and Colonoscopic findings. Patients were followed-up for their clinical response at every visit and the disease activity was assessed by Mayo Score and Simple Clinical Colitis Activity Index (SCCAI). Subjects were continued on their standard of care pharmacotherapy.

Table 2: Mayo Score[51]

A=Stool Frequency 0 = Normal 1 = 1–2 stools/day more than normal 2 = 3–4 stools/day more than normal 3 = >4 stools/day more than normal **B=Rectal Bleeding** 0 = None 1 = Streaks of blood with stool less than half the time 2 = Visible blood with stool half of the time or more 3 = Passing blood alone **C=Physician Global Assesment** 0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease **D=Endoscopic Mayo Score** 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration) MAYO SCORE= A+B+C+D

Clinical Remission was defined as Mayo score of ≤2 with all individual categories ≤1. Clinical response was defined as decrease in Mayo score of at least 3 points from baseline

Table 3: SIMPLE CLINICAL COLITIS ACTIVITY INDEX (SCCAI)[52]

SIMPLE CLINICAL COLITIS ACTIVITY INDEX
Bowel frequency (day) 0=1-3 1=4-6 2=7-9 3=>9
Bowel frequency (night) 1=1-3 2=4-6
Urgency of defecation 1=Hurry 2=Immediately 3=Incontinence
Blood in stools 1= Trace 2= Occasionally frank 3= Usually frank
General well being 0= Very Well 1= Slightly Below Par 2=Poor 3=Very Poor 4=Terrible
Extraintestinal manifestation (1 per manifestation)
TOTAL

INCLUSION CRITERIA

- Age ≥18 years
- Confirmed Active Ulcerative Colitis patients
- Able to give informed consent and/or assent as appropriate

EXCLUSION CRITERIA

- Patients in clinical remission
- Patients having toxic megacolon
- Treatment naïve patients
- Pregnant and lactating ladies
- Prior colectomy
- Positive stool test for any of the following: Clostridium difficile, Salmonella, Shigella, Yersinia, Campylobacter, E. coli by standard stool culture.
- Regular probiotic supplement use within prior 4 weeks to enrollment
- Severe immunodeficiency, inherited or acquired (e.g. HIV, chemotherapy, or radiation therapy)
- Patients unwilling or unable to give consent or participate in all study requirements

INCLUSION CRITERIA FOR DONOR

- Age >18 years
- Score of 2,3 or 4 on Bristol stool scale
- Stool culture and microscopy tests negative for common detectable enteric pathogens (Salmonella, Shigella, Campylobacter, Vibrio parahemolyticus, Vibrio cholera, Candida albicans, E. coli, Clostridium difficile, Entamoeba histolytica, Giardia lamblia, Cryptosporidium, Ascaris lumbricoides, Trematodes/tape worms)
- Negative screening for hepatitis A, anti HCV, HBsAg, syphilis and anti HIV within three months of donation.

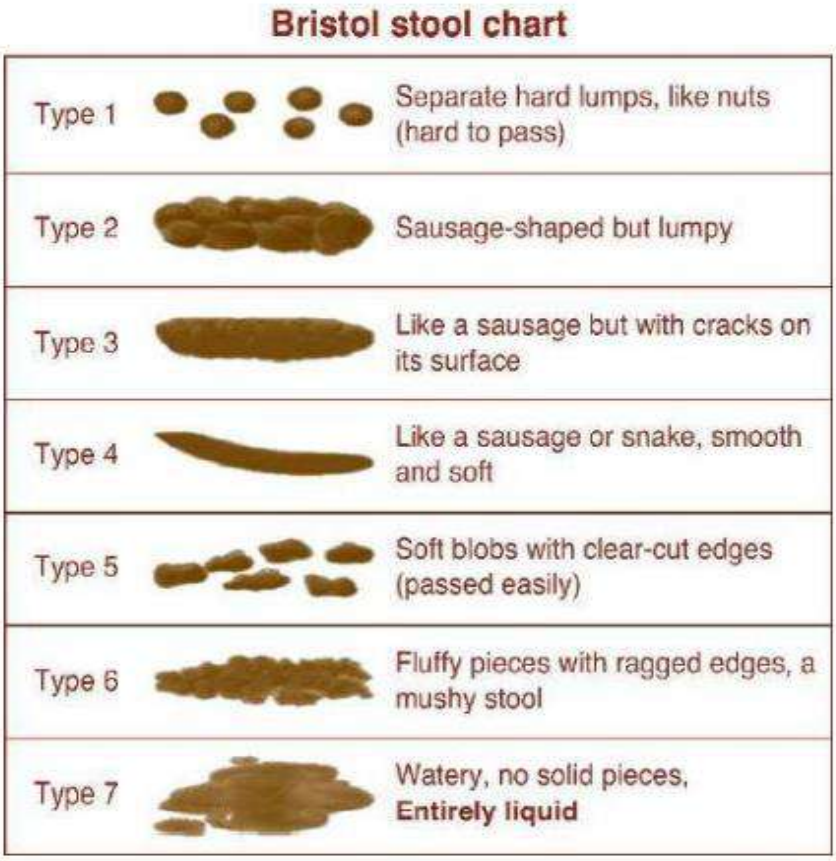
Bristol stool chart
Type 1
Separate hard lumps, like nuts (hard to pass)
Type 2
Sausage-shaped but lumpy
Type 3
Like a sausage but with cracks on its surface
Type 4
Like a sausage or snake, smooth and soft
Type 5
Soft blobs with clear-cut edges (passed easily)
Type 6
Fluffy pieces with ragged edges, a mushy stool
Type 7
Watery, no solid pieces, Entirely liquid

FIG 1: Bristol Stool Chart

EXCLUSION CRITERIA FOR DONOR

- Tattoos or body piercings within the last 6 months
- High-risk sexual behaviors
- Communicable illnesses or antibiotic treatment within the past 3 months
- Intrinsic gastrointestinal illnesses such as irritable bowel syndrome, inflammatory bowel disease, gastrointestinal malignancies or major gastrointestinal surgical procedures.
- Ongoing immune-modulator therapy for any concurrent illness
- A history of chronic pain syndromes (fibromyalgia, chronic fatigue) or neurologic, neurodevelopmental disorders
- Metabolic syndrome, obesity (BMI of >30), or moderate-to-severe undernutrition (malnutrition)
- A history of malignant illnesses or ongoing oncologic therapy

PROTOCOL FOR PERFORMING FMT

Donor preparation

- A gentle osmotic laxative was given the night before procedure
- Donor were instructed to avoid of any food to which the recipient may be allergic for 5 days before the procedure
- Donor were instructed to notify if any symptoms of infection occur between screening and time of donation.

Recipient preparation

- Large volume bowel preparation was given a day before the procedure.

PREPARATION OF STOOL AND ADMINISTRATION

- Stool sample was collected in an airtight container and used within 6 hours of collection.
- Universal precautions were observed while handling the stool.
- Preservative free normal saline was used to dilute the stool sample
- Using a blender, stool was homogenized and diluents added till it reached a liquid consistency.
- Stool was filtered to remove the particulate matter.
- The finished stool slurry was used immediately and administered via colonoscope.

DURATION OF STUDY

The study period lasted from 1st January 2019 till completion of 7 sessions of the last enrolled patient. Last date for enrolment was 30th September 2019. The patients were followed up for a period of 8 months from enrolment.

OUTCOME

Primary outcome

- To determine the number of FMT sessions needed to achieve clinical remission

Secondary outcome

- To determine the number of FMT sessions needed to achieve clinical response
- To determine the number of FMT sessions needed to achieve Simple Clinical Colitis Activity Index (SCCAI) $\leq$1

STATISTICAL ANALYSIS

The clinical response was assessed at every visit. Multivariate analysis was used to find association between the study variable and its correlates. SPSS software was used for statistical analysis.

OBSERVATIONS AND RESULTS

This interventional, prospective and uncontrolled study was conducted on the patients attending the outpatient department or admitted in Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, India. Thirty three patients were enrolled during the study period. Of the thirty-three patients, one patient was lost to follow-up at the second visit, four more patients were lost to follow up at the third visit and one more at the fourth visit. Total six patients were lost to follow-up. Remaining 27 patients completed all 7 sessions of FMT. These patients received FMT through per rectal route with colonoscope reaching up to ileum or as close as possible to caecum. Patients were followed-up for their clinical response and disease activity was assessed by full Mayo Clinic Score and SCCAI.

TABLE 4A: AGE DISTRIBUTION:

AGE (YEARS)	NO OF PATIENTS	PERCENTAGE
11-20	4	12.12%
21-30	13	39.39%
31-40	9	27.27%
41-50	5	15.15%
51-60	2	6.06%
TOTAL	33	100%

Majority of the patients were young adults belonging to the 21-30 years age group (39.39%) followed by the 31-40 years age group.

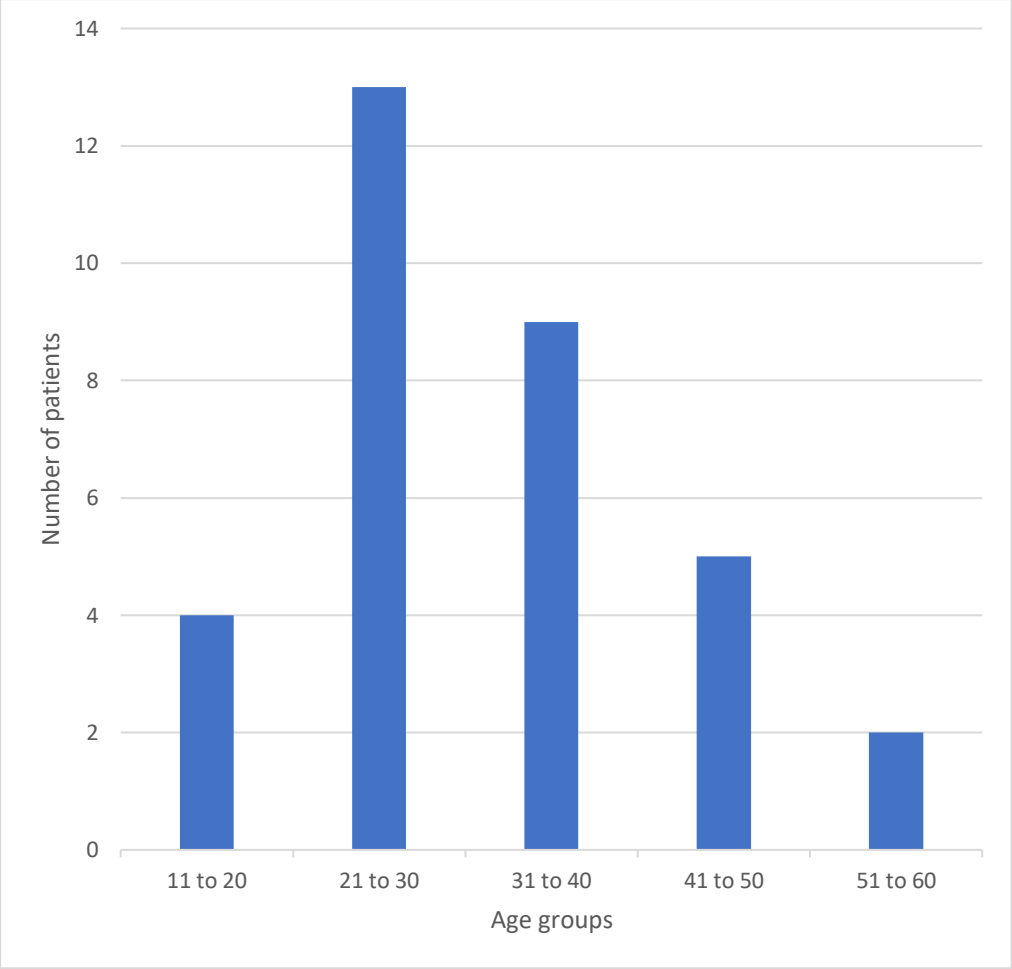

FIG 2: AGE DISTRIBUTION

TABLE 4B: AGE DISTRIBUTION:

	N	Min.	Max.	Mean	Std. Deviation
Age	33	11.0	60.0	32.18	10.58

TABLE 5: GENDER DISTRIBUTION:

GENDER	No. of cases	Percentage
Female	19	57.6%
Male	14	42.4%
Total	33	100.0%

The study comprised of 19 (57.6%) females and 14 (42.4%) males, with a M:F ratio of 0.73

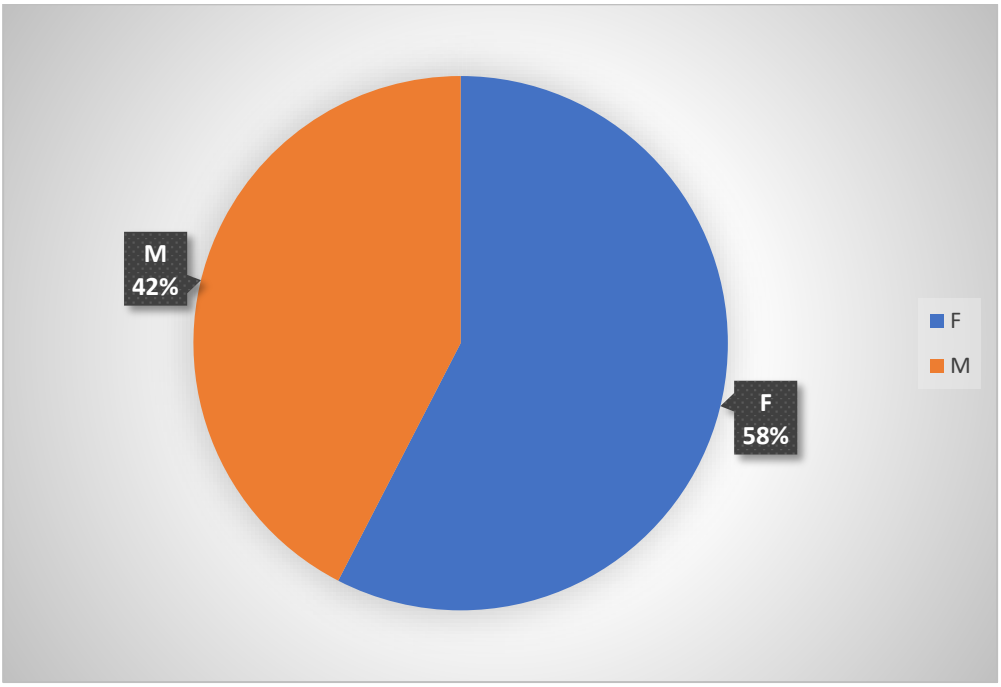

FIG 3: GENDER DISTRIBUTION

TABLE 6A: DISEASE DURATION:

Disease duration (years)	No. of patients	Percentage
0-5	24	72.73
5-10	7	21.21
>10	2	6.06
Total	33	100

Majority of the people had a disease duration of less than 5 years (72.73%) while 6.06% had a disease duration of >10 years

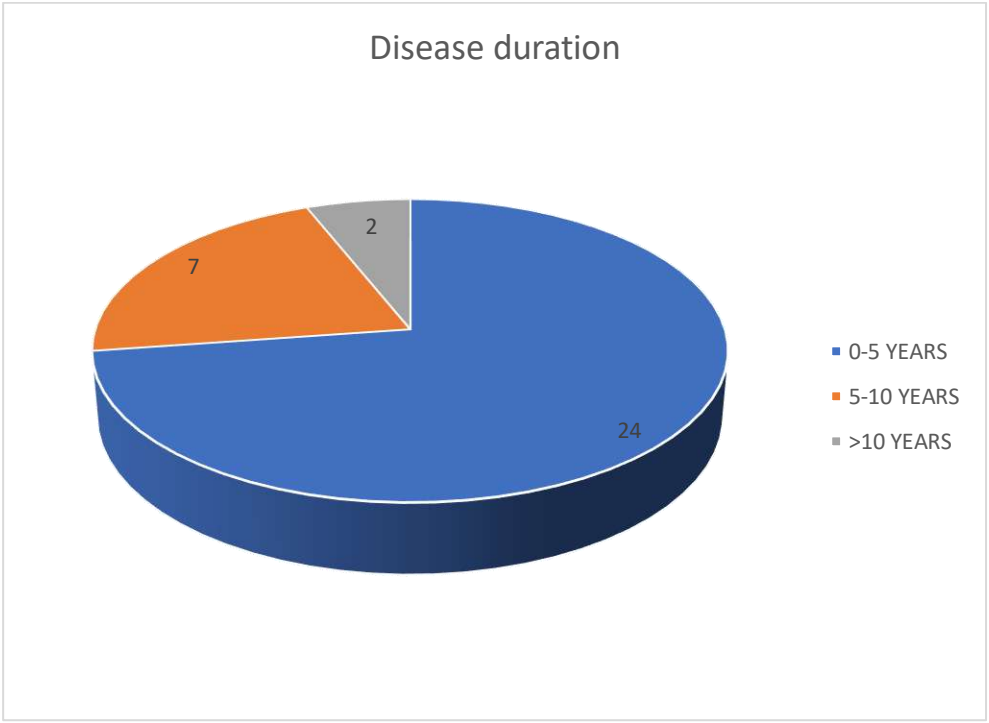

FIG 4: DISEASE DURATION IN YEARS

TABLE 6B: DISEASE DURATION

	N	Minimum	Maximum	Mean	Std. Deviation
Disease Duration	33	0.3	17.0	3.26	3.85

The Range of disease duration was around 2 months to 17 years with a median of 2 years, mean disease duration was 3.26 years with a standard deviation of 3.85 years.

TABLE 7A: BMI

	N	Minimum	Maximum	Mean	Std. Deviation
BMI	33	18.1	28.6	21.95	2.40

Mean body mass index of subjects was 21.9 ± 2.40 kg/m^2

Table 7B: BMI

BMI (kg/m^2)	NO OF PATIENTS	PERCENTAGE
<18.5	1	3.03
18.5-22.9	25	75.76
23-25	3	9.09
>25	4	12.12
TOTAL	33	100

75.76% of patients had normal BMI while one patient was underweight. 21.21% patients were overweight.

TABLE 8: COMORBIDITIES:

Co-morbidities	No. of cases	Percentage
BRONCHIAL ASTHMA	1	3.0%
CELIAC DISEASE	1	3.0%
HYPOTHYROIDISM	1	3.0%
NO COMORBIDITY	30	90.9%
TOTAL	33	100.0%

3 of the 33 (9%) patients had a history of comorbidities.

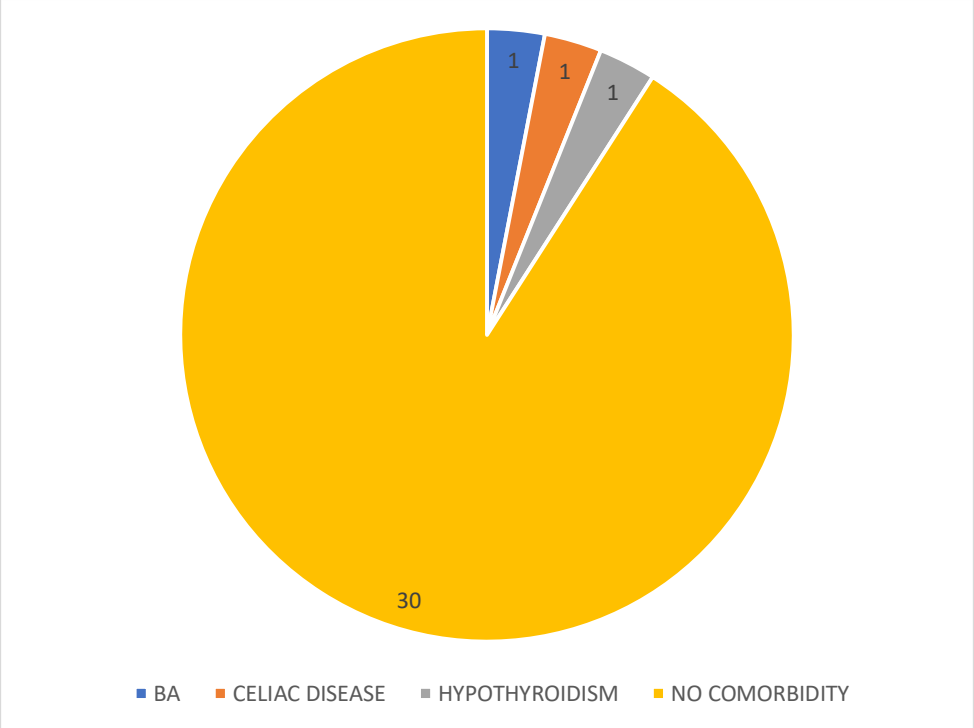

FIG 5: COMORBIDITIES

None of the patients enrolled had a positive family history of inflammatory bowel disease, neither any of the patients had undergone appendicectomy in past. None of the patients had any history of

Alcohol, Smoking or Opium abuse, neither did any of them have a history of Intravenous Drug Abuse

TABLE 9A: PREVIOUS EXPOSURE TO BIOLOGICALS AND IMMUNOMODULATORS:

Previous Biologicals	No. of cases	Percentage
NO	31	93.9%
YES	2	6.1%
Total	33	100.0%

TABLE 9B: CONCURRENT IMMUNOMODULATORS

Previous Immunomodulators	No. of patients	Percentage
AZT 100mg	8	24.24
AZT 25 mg	3	9.09
AZT 50mg	1	3.03
AZT 75mg	1	3.03
No	20	60.61
Total	**33**	**100.00**

2 patients (6.1%) had exposure to Biologicals (Infliximab and Adalimumab) in the past whereas 13 patients (39.39%) had exposure to immunomodulators (Azathioprine). All patients had exposure to 5-ASA compounds. None of the patients had received Cyclosporine/ Tacrolimus in the past.

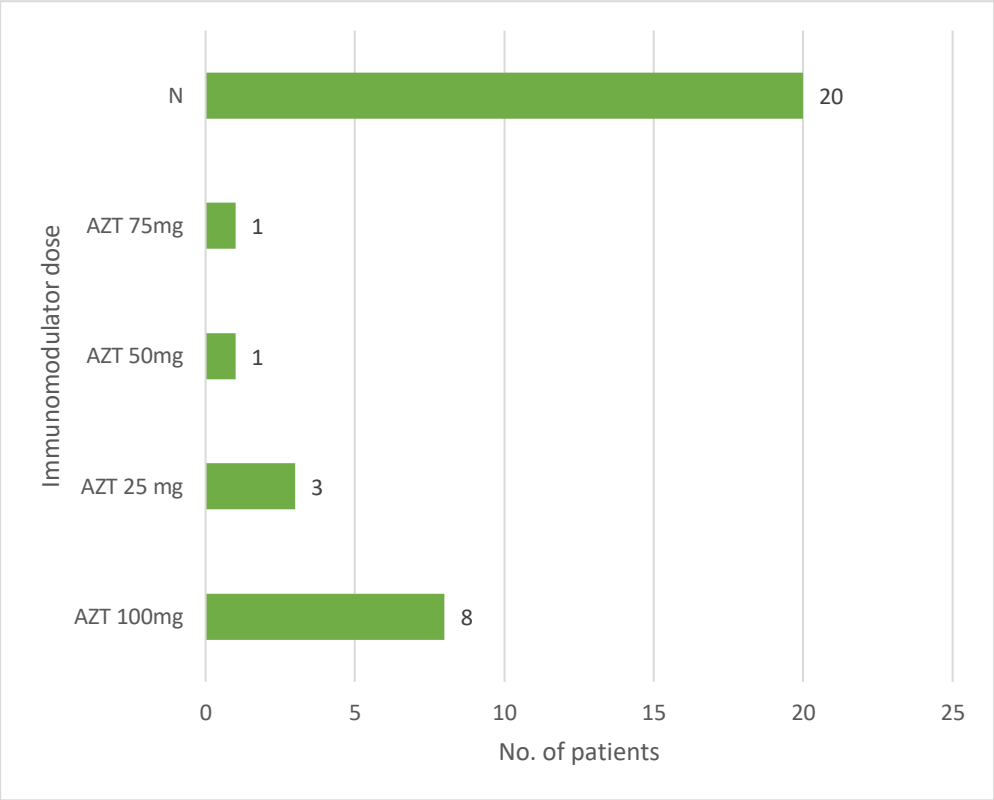

FIG 6: CONCURRENT IMMUNOMODULATORS

TABLE 10A: EXPOSURE TO ORAL STEROIDS

Exposure to oral steroids	No. of patients	Percentage
N	4	12.12%
Y	29	87.88%
Total	**33**	**100.00%**

TABLE 10B: EXPOSURE TO I.V. STEROIDS

Exposure to I.V. steroids	No. of patients	Percentage
N	26	78.79%
Y	7	21.21%
Total	**33**	**100.00%**

Almost 88% (29/33) patients had previously taken oral steroids, however only 21.21% (7/33) of patients had previous exposure to I.V. Steroids.

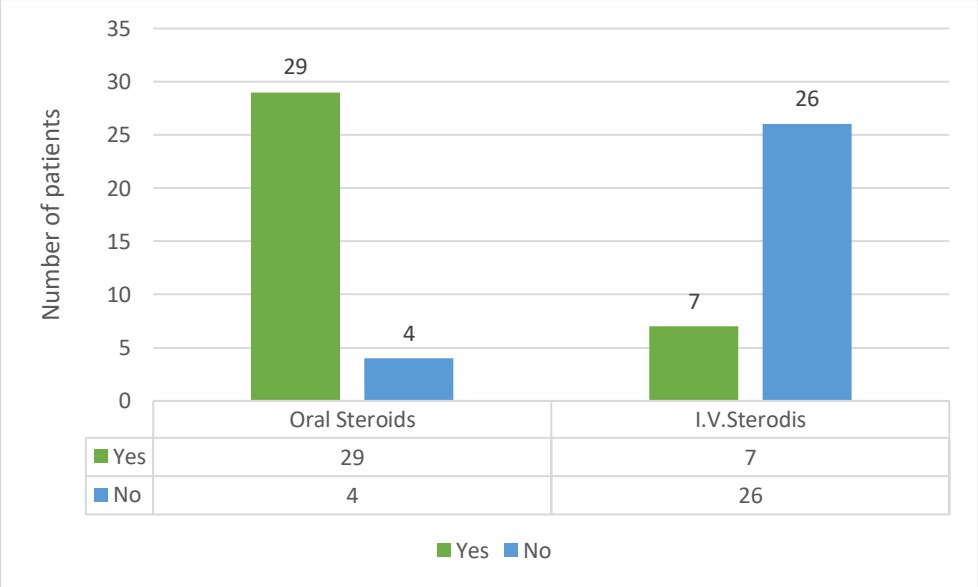

FIG 7: EXPOSURE TO STEROIDS

TABLE 11: RETENTION TIME:

Retention time	N	Minimum	Maximum	Mean	Std. Deviation
Visit 1	33	0.2	5.0	2.54	1.35
Visit 2	32	0.5	5.0	3.39	1.38
Visit 3	28	1.0	6.0	4.32	1.09
Visit 4	27	2.0	7.0	4.79	1.02
Visit 5	27	0.3	6.0	4.59	1.24
Visit 6	27	1.0	6.0	4.68	1.15
Visit 7	27	2.0	6.0	4.81	0.73

The mean retention time at the first visit was 2.54 $\pm$ 1.35 hours, which progressively increased to 4.79 $\pm$ 1.02 hours at the 4th visit and remained high around 4.81 $\pm$ 0.73 hours at the 7th visit. The patients were instructed to retain the faecal slurry for as long as possible.

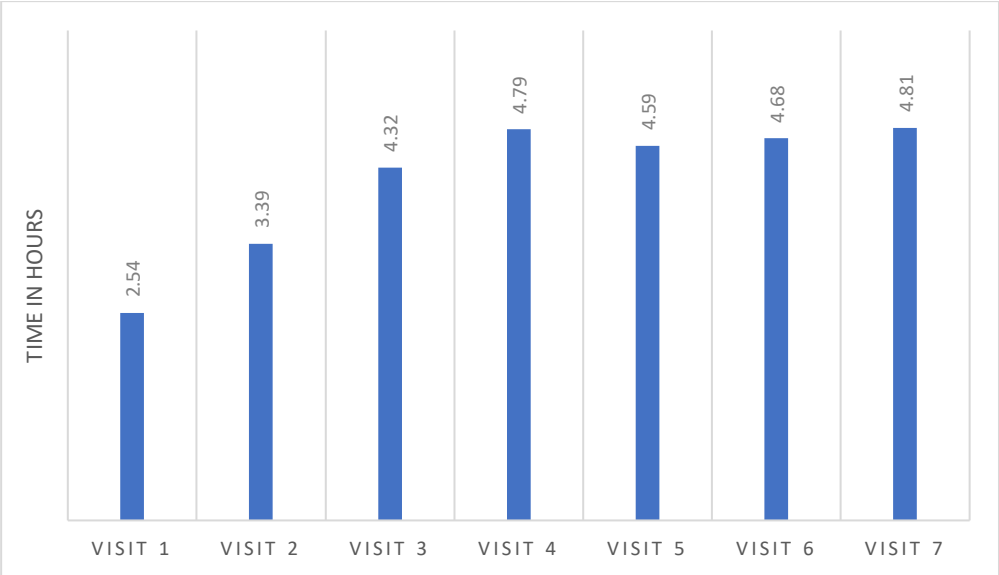

FIG 8: MEAN RETENTION TIME

TABLE 12: MAYO SCORE--NUMBER OF STOOLS:

NUMBER OF STOOLS	N	Min.	Max.	Mean	Std. Deviation
Visit 1	33	0.0	3.0	2.03	0.79
Visit 2	32	0.0	3.0	1.31	0.82
Visit 3	28	0.0	2.0	0.71	0.76
Visit 4	27	0.0	2.0	0.52	0.75
Visit 5	27	0.0	2.0	0.37	0.74
Visit 6	27	0.0	2.0	0.30	0.61
Visit 7	27	0.0	2.0	0.30	0.61

The mean Score for the Number of stools as per Mayo score at the first visit was 2.03 $\pm$ 0.79 which gradually decreased to 0.3 $\pm$ 0.6 at the 7th visit.

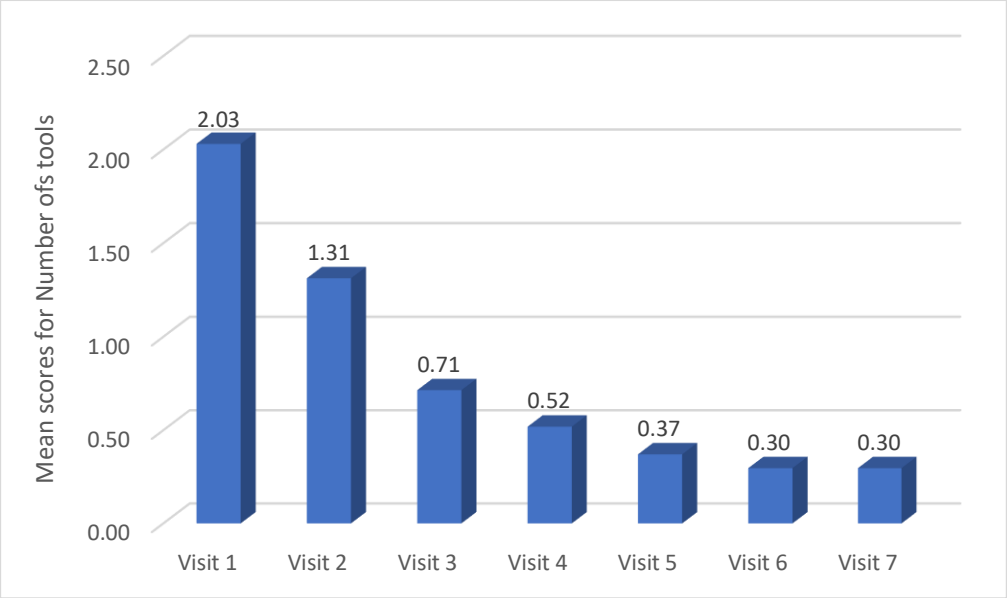

FIG 9: MAYO SCORE- NUMBER OF STOOLS

TABLE 13: MAYO SCORE-BLOOD IN STOOLS:

BLOOD IN STOOLS	N	Minimum	Maximum	Mean	Std. Deviation
Visit 1	33	0.0	2.0	0.79	0.65
Visit 2	32	0.0	1.0	0.16	0.37
Visit 3	28	0.0	0.0	0.00	0.00
Visit 4	27	0.0	0.0	0.00	0.00
Visit 5	27	0.0	0.0	0.00	0.00
Visit 6	27	0.0	1.0	0.04	0.19
Visit 7	27	0.0	1.0	0.04	0.19

The mean score for the Blood in stools as per Mayo score at the first visit was 0.79± 0.65 which decreased to 0 at the 4th visit however increased again to 0.04± 0.19 at the 7th visit.

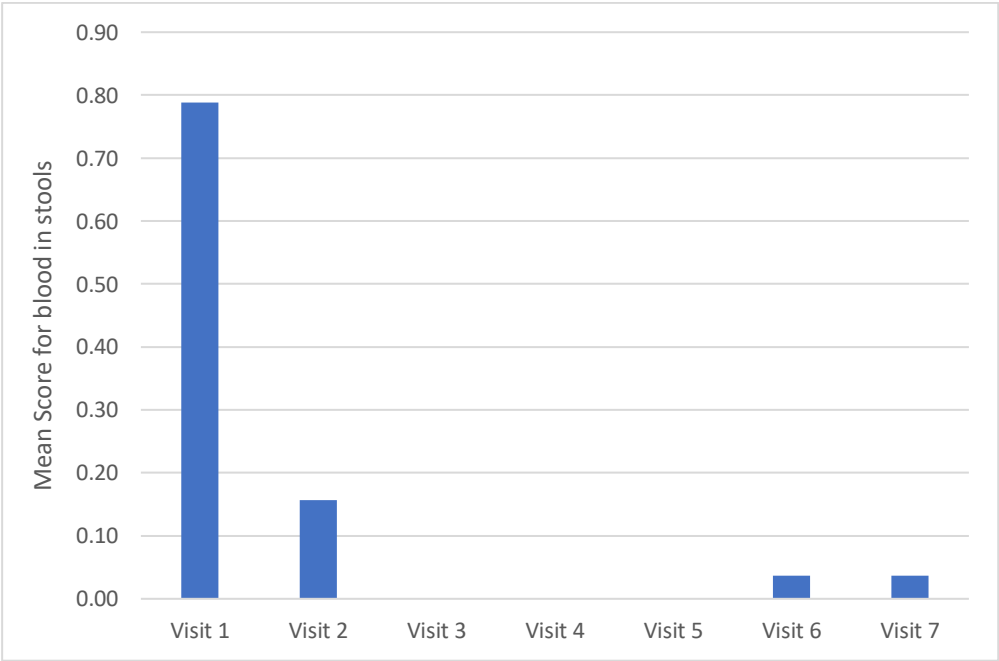

FIG 10: MAYO SCORE- BLOOD IN STOOLS

TABLE 14A: ENDOSCOPIC MAYO SCORE

Endoscopic Mayo Score	N	Min.	Max.	Mean	Std. Deviation
Visit 1	33	1.0	3.0	2.61	0.61
Visit 2	32	0.0	3.0	1.75	1.05
Visit 3	28	0.0	3.0	1.50	0.92
Visit 4	27	0.0	3.0	1.04	1.02
Visit 5	27	0.0	2.0	0.70	0.82
Visit 6	27	0.0	3.0	0.85	0.86
Visit 7	27	0.0	3.0	0.70	0.87

The Mean Endoscopic Mayo score at the first FMT session was 2.61 ± 0.6 which gradually declined to 1.04 ± 1.02 at visit 4 and to 0.70 ± 0.87 at visit 7.

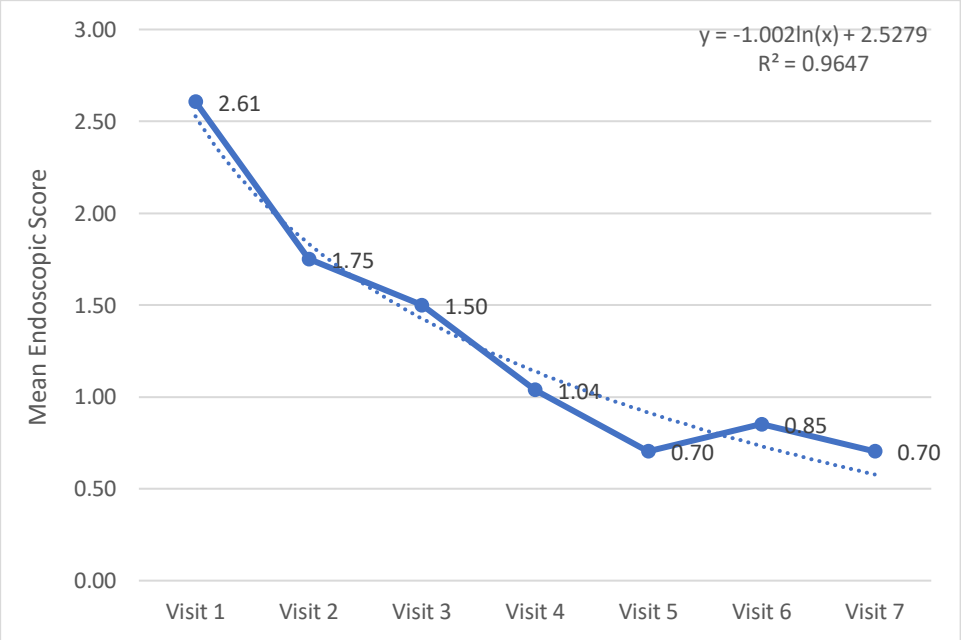

FIG 11: ENDOSCOPIC MAYO SCORE

TABLE 14B: COMPARISON OF ASSOCIATION OF ENDOSCOPIC MAYO SCORE OVER TIME TENDS USING MANN KENDALL TEST

	N	Mean	Std. Deviation	Min.	Max.	Mean Rank	Kendall's W; P value
VISIT 1	27	2.59	0.636	1	3	6.33	0.541; <0.01
VISIT 2	27	1.74	1.023	0	3	5.02	
VISIT 3	27	1.56	0.892	0	3	4.80	
VISIT 4	27	1.04	1.018	0	3	3.59	
VISIT 5	27	0.70	0.823	0	2	2.78	
VISIT 6	27	0.85	0.864	0	3	2.98	
VISIT 7	27	0.70	0.869	0	3	2.50	

The analysis of trend of the Endoscopic Mayo score using the Mann Kendall test was done on 27 patients as 6 patients were lost to follow up and failed to complete the entire protocol. As depicted in table no. 11B, there was a significant positive association of the Mayo score with increasing FMT sessions with a Kendall coefficient coefficient value of 0.541 and p value of <0.01.

TABLE 15: DISEASE SEVERITY AT BASELINE:

	Mayo Score	No. of patients	Percentage
Mild	3-5	9	27.27
Moderate	6-10	22	66.67
Severe	>11	2	6.06
Total		33	100

9 patients of 33 (27.2%) had mild disease at baseline with a Mayo score of 3-5, 22/33(66.67%) patients had a moderately severe disease with a Mayo score of 6-10, while 2 patients had a severe disease on presentation.

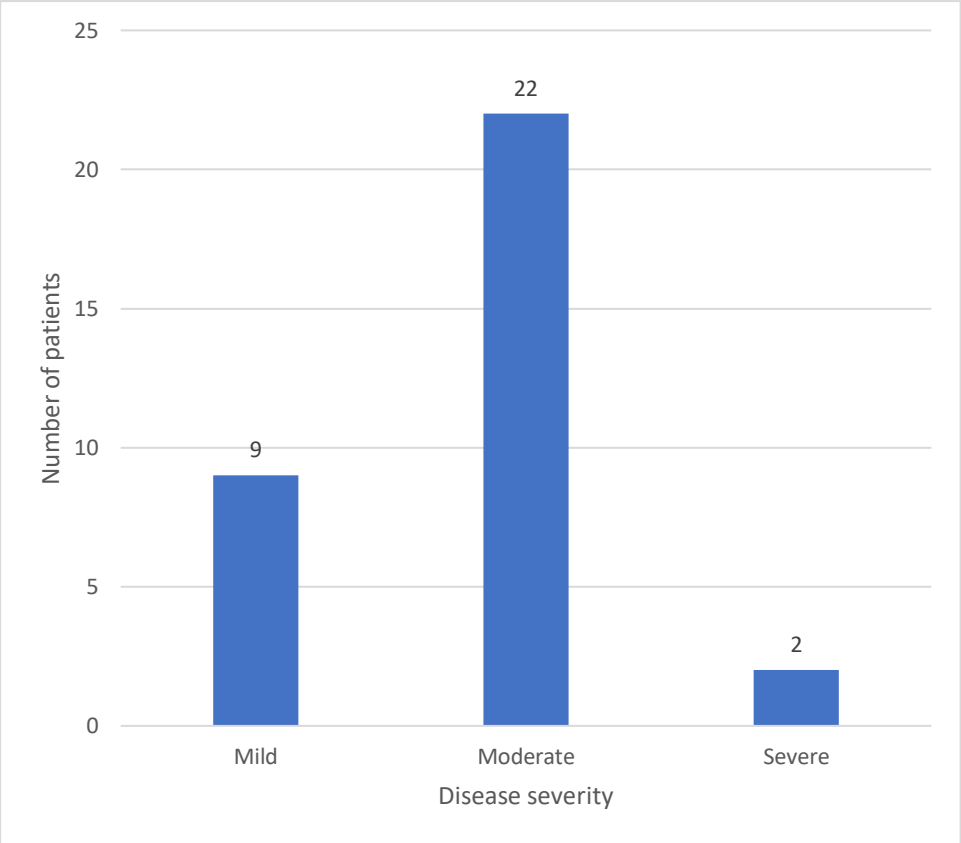

FIG 12: DISEASE SEVERITY AT BASELINE

TABLE 16A: TOTAL MAYO SCORE

Total Mayo Score	N	Min.	Max.	Mean	Std. Deviation
Visit 1	33	4.0	11.0	7.24	1.90
Visit 2	32	1.0	9.0	4.47	2.11
Visit 3	28	1.0	7.0	3.36	1.77
Visit 4	27	1.0	7.0	2.63	1.74
Visit 5	27	1.0	6.0	2.11	1.48
Visit 6	27	1.0	7.0	2.30	1.71
Visit 7	27	1.0	7.0	2.07	1.59

The mean total Mayo score at visit 1 was 7.24 ± 1.90 which improved over the next sessions to 2.11 ± 1.48 at visit 5 and remained at 2.07 ± 1.59 at visit 7.

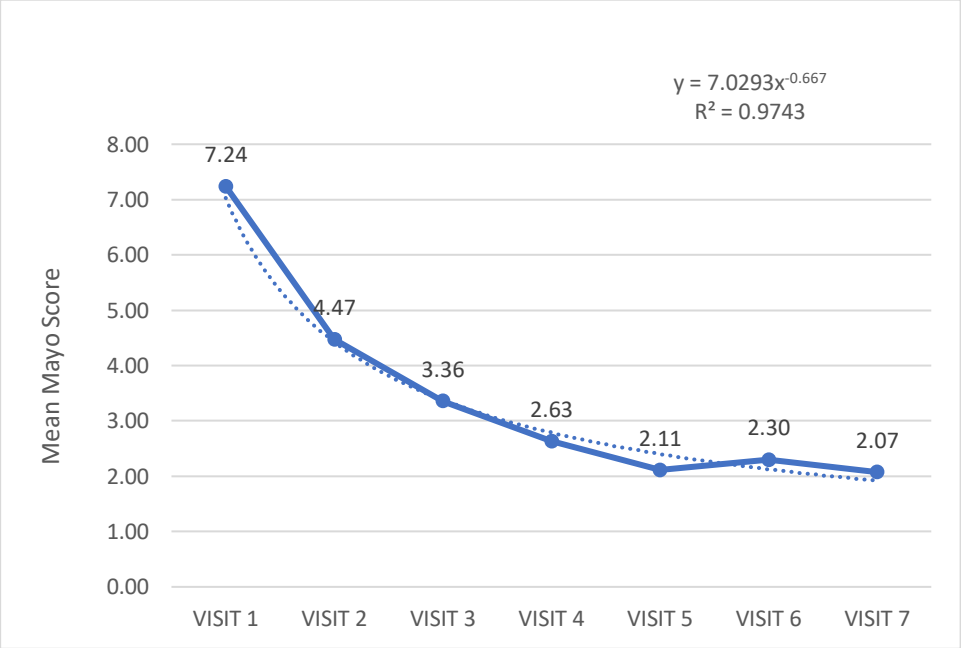

FIG 13: MEAN MAYO SCORE

The above results on a Power trendline have a significant R^2value of 0.9743

TABLE 16B: COMPARISON OF ASSOCIATION OF MAYO SCORE OVER TIME TENDS USING MANN KENDALL TEST

	N	Mean	Std. Deviation	Min.	Max.	Mean Rank	Kendall's W; P value
VISIT 1	27	7.30	1.73	5.00	11.00	6.91	0.707; <0.01
VISIT 2	27	4.52	2.007	1	9	5.46	
VISIT 3	27	3.44	1.739	1	7	4.46	
VISIT 4	27	2.63	1.735	1	7	3.35	
VISIT 5	27	2.11	1.476	1	6	2.74	
VISIT 6	27	2.30	1.706	1	7	2.78	
VISIT 7	27	2.07	1.591	1	7	2.30	

The association of Mayo Score trend with each visit of FMT was analysed using Mann Kendall test. As depicted in table no. 12B, there was a significant positive association of the Mayo score with Seven FMT sessions with a Kendall coefficient coefficient value of 0.707 and p value of <0.01.

TABLE 16C: COMPARISON OF THE KENDALL COEFFICIENT OF CONCORDANCE AT DIFFERENT VISITS:

Visit	Kendall's W
Visit 1-4	0.843
Visit 1-5	0.821
Visit 1-6	0.770
Visit 1-7	0.707

The Kendall coefficient coefficient value progressively decreases after the 4th visit onwards.

TABLE 16D: POST HOC ANALYSIS OF THE MEAN MAYO SCORE TREND

Score 1- score 2	Test statistic	Std. Test Statistic	P -value
Visit 1- 2	1.455	2.735	0.131
Visit 1- 3	2.636	4.957	<0.01
Visit 1- 4	3.64	6.84	<0.01
Visit 2- 3	1.18	2.222	0.552
Visit 2 -4	2.182	4.103	0.001
Visit 4- 5	0.5	0.94	1.00
Visit 4- 6	0.470	0.883	1.00
Visit 4- 7	0.864	1.624	1.00
Visit 6-5	-0.30	-0.57	1.00
Visit 7-5	0.364	0.684	1.00
Visit 7-6	0.394	0.741	1.00

The above table indicates the post Hoc analysis of the trend of Mayo score over the seven visits. The p values of the mean Mayo score between two groups of Visit 1- Visit 2, Visit 1-visit 3, Visit 1-Visit 4, Visit 2-visit 4 are significant (<0.05). Also, the P values of the mean Mayo score between the groups of Visit 4- Visit 5, Visit 4-visit 6, Visit 4-Visit 7, Visit 5-visit 6, Visit 5- Visit 7 and Visit 6- visit 7 are not significant. This, along with the progressive decrease in the Kendall Coefficient value from visit 4 onwards (as indicated in Table12C),indicates that the benefit in Mayo score after the 4^{th} visit of FMT may not be statistically significant.

TABLE 17: CLINICAL REMISSION

	Visit 1		**Visit 2**		**Visit 3**		**Visit 4**		**Visit 5**		**Visit 6**		**Visit 7**	
Total Mayo score	No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage
> 2	33	100.0%	27	84.4%	17	60.7%	10	37.0%	7	25.9%	7	25.9%	6	22.2%
≤ 2	0	0.0%	5	15.6%	11	39.3%	17	63.0%	20	74.1%	20	74.1%	21	77.8%
Total	33	100.0%	32	100.0 %	28	100.0 %	27	100.0 %	27	100.0 %	27	100.0 %	27	100.0 %

The proportion of patients achieving Clinical remission (defined as Mayo score of ≤2 with all individual categories ≤1) was 15.6% at visit 2. It progressively increased to 39.3% (11/28) at visit 3, 63% (17/27) at visit 4, 74.5% (20/27) at visits 5 and 6 and 77.8% (21/27) at visit 7.

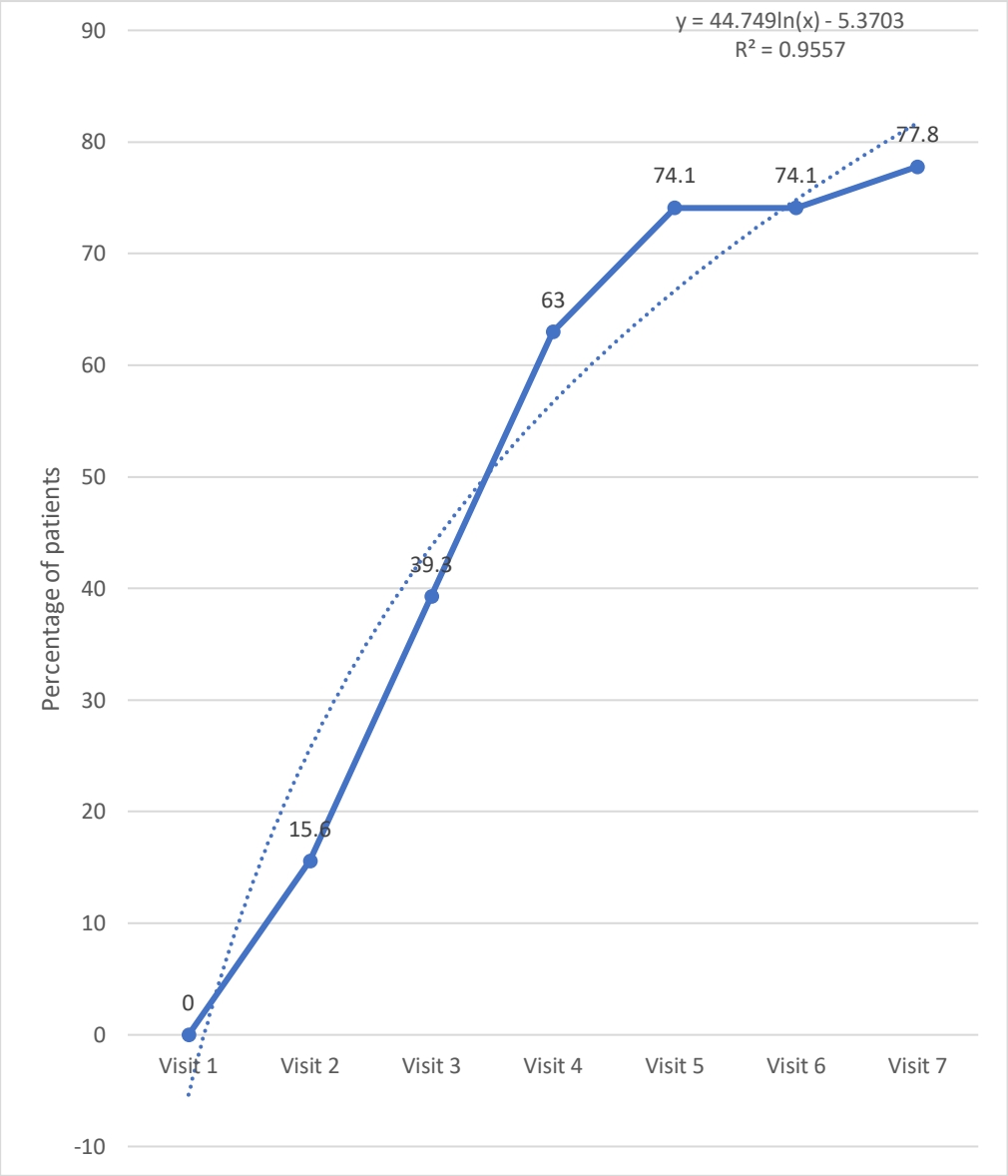

FIG 14: PROPORTION OF PATIENTS WITH CLINICAL REMISSON AT EACH VISIT

TABLE 18: ENDOSCOPIC REMISSION

	Visit 1		Visit 2		Visit 3		Visit 4		Visit 5		Visit 6		Visit 7	
Endoscopic remission	**No. of cases**	**%**	**No. of cases**	**%**	**No. of cases**	**%**	**No. of cases**	**%**	**No. of cases**	**%**	**No. of cases**	**%**	**No. of cases**	**%**
NO	31	93.9	20	62.5	14	50.0	8	29.	6	22.2	6	22.2	8	29.6
YES	2	6.1	12	37.5	14	50.0	19	70.4	21	77.8	21	77.	22	81.5
Total	33	100.0	32	100.0	28	100.0	27	100.0	27	100.0	27	100.0	27	100.0

On a per protocol analysis the proportion of patients achieving Endoscopic remission (defined as a Endoscopic Mayo subscore of $\leq$1) was 37.5% at the second visit, increased to 70.4% at visit 4 and 81.5% at visit 7.

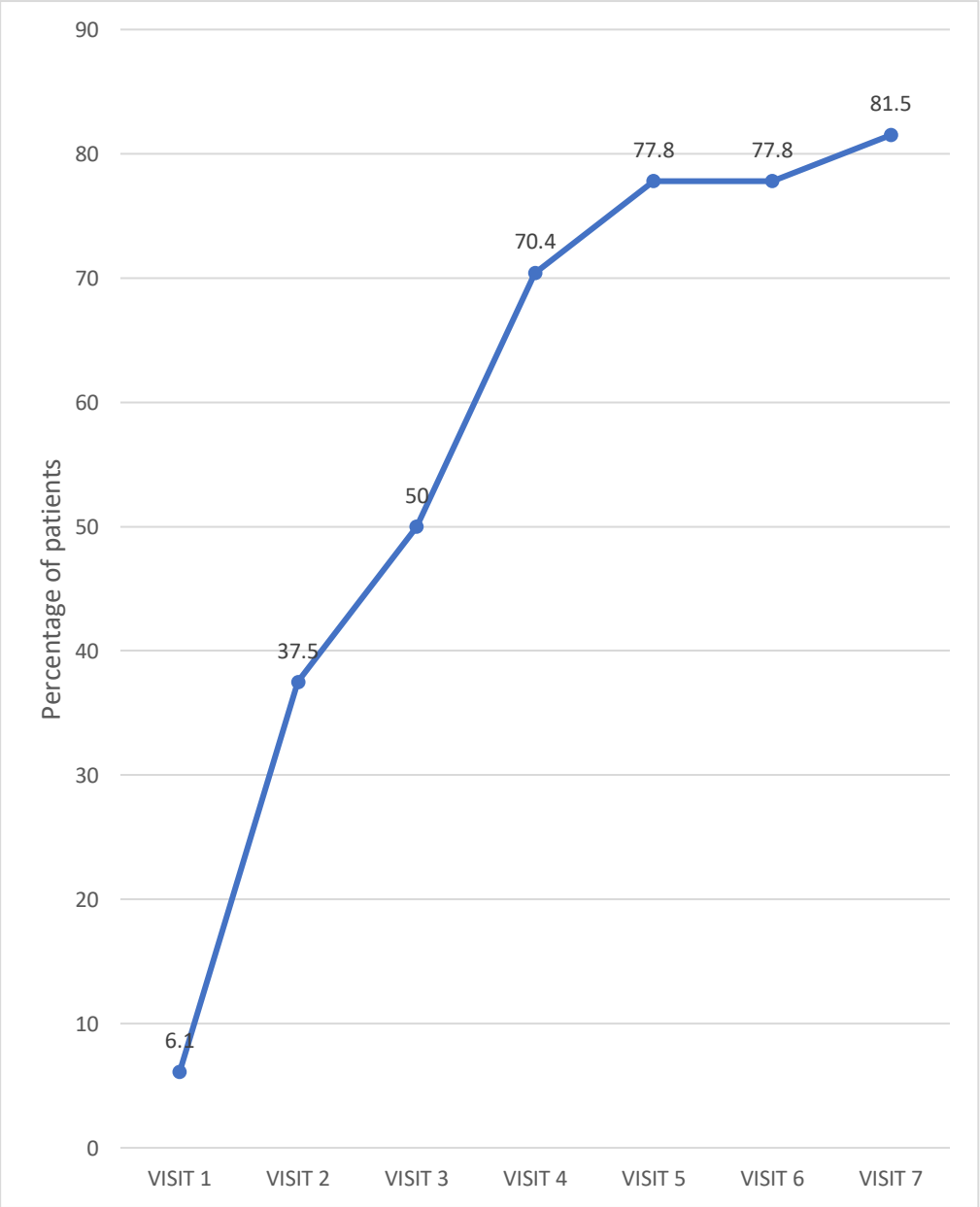

FIG 15: PROPORTION OF PATIENTS WITH ENDOSCOPIC REMISSION

TABLE 19: CLINICAL RESPONSE

	Visit 1		Visit 2		Visit 3		Visit 4	
	No. of cases	**Percentage**	**No. of new cases**	**Percentage**	**No. of new cases**	**Percentage**	**No. of cases**	**Percentage**
CLINICAL RESPONSE	0	0.0	18	56.3	7	25.0	6	22.2
Total	33	100.0	32	100.0	28	100.0	27	100.0

Of the 33 cases, 18 patients (56.3%) achieved clinical response (defined as decrease of at least 3 points from baseline) at the 2nd visit, 7 patients (25%) at the 3rd visit and 6 patients (22.2%) achieved it at the 4th visit. Three patients failed to complete the study protocol before achieving clinical response.

TABLE 20A: SIMPLE CLINICAL COLITIS ACTIVITY INDEX

SCCAI	N	Min.	Max.	Mean	Std. Deviation
Visit 1	33	1.0	12.0	7.21	2.52
Visit 2	32	1.0	10.0	3.68	2.00
Visit 3	28	0.0	5.0	1.89	1.49
Visit 4	27	0.0	6.0	1.37	1.57
Visit 5	27	0.0	5.0	1.07	1.68
Visit 6	27	0.0	7.0	0.88	1.82
Visit 7	27	0.0	7.0	0.96	1.93

The mean SCCAI score at the 1st visit were 7.21 ± 2.52, they improved over the course of the next visits to 1.37± 1.57 at the 4th visit and 0.96 ± 1.93 at the 7th visit. The trend of SCCAI over time had a significant R^2value of 0.979.

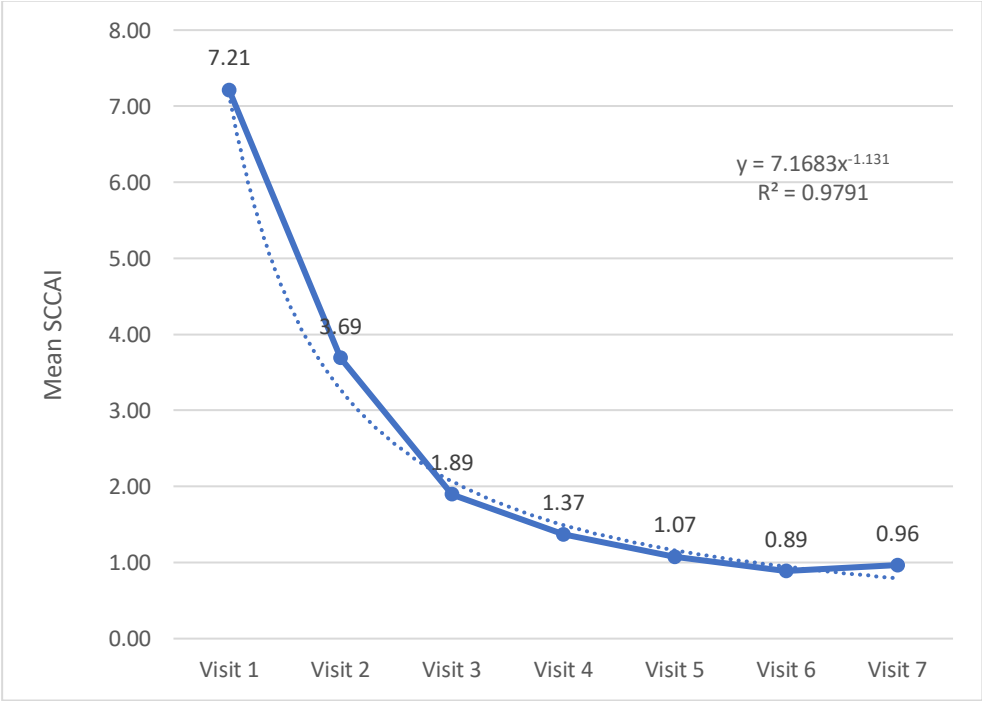

FIG 16A: SIMPLE CLINICAL COLITIS ACTIVITY INDEX

TABLE 20B: SCCAI

	Visit 1		Visit 2		Visit 3		Visit 4		Visit 5		Visit 6		Visit 7	
SCCAI	**No. of cases**	**%**	**No. of cases**	**%**	**No. of cases**	**%e**	**No. of cases**	**%**	**No. of cases**	**%**	**No. of cases**	**%**	**No. of cases**	**%**
>1	32	97.0	30	93.8	18	64.3	11	40.7	8	29.6	6	22.2	6	22.2
≤ 1	1	3.0	2	6.3	10	35.7	16	59.3	19	70.4	21	77.8	21	77.8
Total	33	100.0	32	100.0	28	100.0	27	100.0	27	100.0	27	100.0	27	100.0

SCCAI scores of ≤ 1 were achieved in 1/33 (3%), 2/32(6.3%), 10/28 (35.7%), 16.27 (59.3%), 19/27 (70.4%), 21/27 (77.8%) and 21/27(77.8%) patients at visits 1,2 ,3,4,5,6 and 7 respectively.

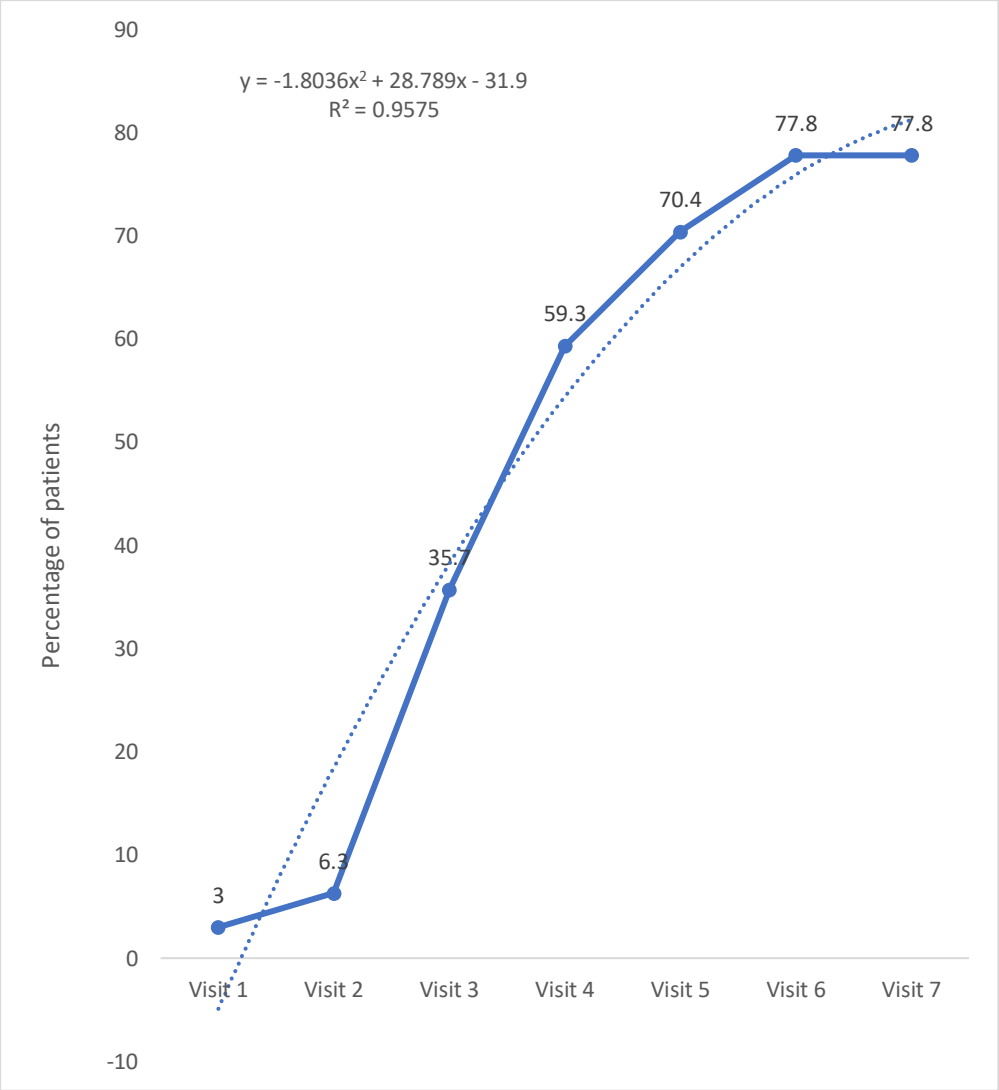

FIG 16B: Proportion of patients with SCCAI ≤ 1 at every visit

TABLE 20C: COMPARISON OF ASSOCIATION OF SCCAI SCORE OVER TIME TENDS USING MANN KENDALL TEST

	N	Mean	Std. Deviation	Min.	Max.	Mean Rank	Kendall's W; P value
VISIT 1	27	7.33	2.253	3	12	6.96	0.716; <0.01
VISIT 2	27	3.70	1.996	1	10	5.63	
VISIT 3	27	1.96	1.480	0	5	4.13	
VISIT 4	27	1.37	1.573	0	6	3.31	
VISIT 5	27	1.07	1.685	0	5	2.85	
VISIT 6	27	0.89	1.826	0	7	2.56	
VISIT 7	27	0.96	1.931	0	7	2.56	

The association of SCCAI trend with each visit of FMT was analysed using Mann Kendall test. As depicted, there was a significant positive association of the SCCAI with increasing FMT sessions with a Kendall coefficient value of 0.716 and p value of <0.01

TABLE 21: EXTENT OF DISEASE

	Visit 1		Visit 2		Visit 3		Visit 4		Visit 5		Visit 6		Visit 7	
Disease extent 1	**No. of cases**	**%**	**No. of cases**	**%**	**No. of cases**	**%**	**No. of cases**	**%**	**No. of cases**	**%**	**No. of cases**	**%**	**No. of cases**	**%**
E1	8	24.2	6	18.8	5	17.9	5	18.5	5	18.5	5	18.5	3	11.1
E2	17	51.5	15	46.9	15	53.6	9	33.3	7	25.9	10	37.0	9	33.3
E3	8	24.2	6	18.8	4	14.3	3	11.1	1	3.7	1	3.7	1	3.7
ER	0	0.0	5	15.6	4	14.3	10	37.0	14	51.9	11	40.7	14	51.9
Total	33	100.0	32	100.0	28	100.0	27	100.0	27	100.0	27	100.0	27	100.0

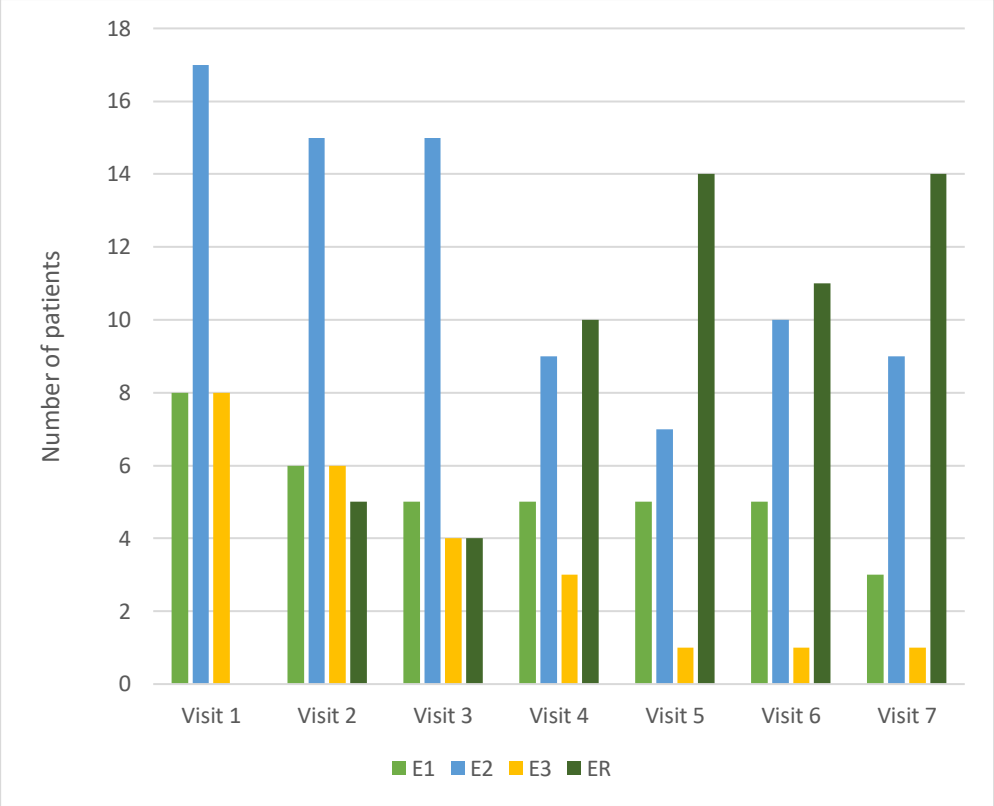

FIG 17: EXTENT OF DISEASE

TABLE 22: ADVERSE EFFECTS

		VISIT 1		VISIT 2		VISIT 3		VISIT 4		VISIT 5		VISIT 6		VISIT 7	
		NO. OF CASES	%	NO. OF CASES	%	NO. OF CASES	%	NO. OF CASES	%	NO. OF CASES	%	NO. OF CASES	%	NO. OF CASES	%
BLOATING		2	6.1	2	6.3	0	0.0	7	25.9	7	25.9	1	3.7	0	0.0
BORBORYGMI		11	33.3	11	34.4	9	32.1	2	7.4	9	33.3	5	18.5	3	11.1
FLATULENCE		6	18.2	12	37.5	11	39.3	6	22.2	4	14.8	3	11.1	5	18.5
PAIN ABDOMEN		13	39.4	5	15.6	2	7.1	2	7.4	3	11.1	0	0.0	0	0.0
PERIANAL PAIN		1	3.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
RECTAL IRRITATION/PAIN		1	3.0	0	0.0	1	3.6	1	3.7	0	0.0	1	3.7	0	0.0
NIL		1	3.0	2	6.3	2	7.1	7	25.9	8	29.6	17	63.0	19	70.4
WORSENING OF DIARRHOEA		0	0.0	0	0.0	1	3.6	0	0.0	0	0.0	0	0.0	0	0.0
MYOPATHY		0	0.0	0	0.0	0	0.0	1	3.7	0	0.0	0	0.0	0	0.0
MENORRHAGIA		0	0.0	0	0.0	1	3.6	1	3.7	0	0.0	0	0.0	0	0.0
TOTAL			33		32		28		27		27		27		27

None of the patients had significant adverse event after FMT. The most common visits were Bloating, pain abdomen and Flatulence on the day of procedure. These were transient and improved over next 24-48 hours with symptomatic therapy. None of the patients had to be hospitalised for the adverse events. One patient experienced transient worsening of diarrhoea which was managed conservatively.

DISCUSSION

There has been considerable interest in the last decade regarding the use of Faecal Microbiota Transplantation as a novel therapeutic option in the management of Ulcerative Colitis. FMT has been postulated to target the dysbiosis in the colonic microbiome and reduce gut inflammation in Ulcerative Colitis. The efficacy of FMT in induction of remission in moderate-severe active UC has been addressed by four randomized controlled trials (RCTs)[39-42]. There has been one RCT pertaining to the use of FMT in the maintenance of remission in UC[44]. FMT has been shown to be effective in patients with steroid dependent UC and steroid refractory UC[45,48].

The results obtained in their RCTs have been conflicting. The difference may be attributed to the composition of the donor's microbiome, genetic build-up of the recipient and the differences in the delivery routes, number of FMT infusions and the interval between two FMT sessions. The role of FMT in active UC is still in a "transition zone" between experimental research and standard of care and further studies are needed to define the optimal timing, optimal dosing frequency, route of delivery, role of antibiotic preconditioning, and donor selection for each patient, as well as its long-term safety and efficacy.

It was reported that five patients with moderate-to-severe active UC were followed up for 3 months after FMT, and for most of them, their gut microbiota was changed by FMT in the first 3 days, but then reverted to the initial state in 1 to 4 weeks in some patients while in others it persisted over at least 12 weeks[37]. It has also been reported, albeit in a paediatric study, that IBD patients require several FMTs to stabilize the altered intestinal microbiota[38]. It has been postulated that continuous FMT could promote intestinal regulation, alter the host immune status and the intestinal barrier, and improve the clinical response to drugs. However, the exact duration of FMT or the number of cycles of FMT to be administered are still not determined. This study aims to establish the pattern of response to multiple FMT sessions in

an attempt to provide an insight regarding optimal route of delivery and number of FMT sessions in the management of active Ulcerative Colitis.

This was an interventional, prospective and uncontrolled study. Consecutive patients with active UC were enrolled in the study and received FMT through per rectal route with colonoscope reaching up to ileum or as close as possible to caecum. Majority of the patients in our study were young adults with 21 of the 33 patients (63.6%) of patients in the 21–40year-old age group. The mean age of patients in our study was 32.12 years. Our study had 19 (57.6%) females and 14 (42.4%) males. In European and North American studies, UC is reported to be equally frequent in men and women at all ages, while CD has consistently revealed a greater incidence in women[53]. In an Indian study, a slight male preponderance was noted in both UC and CD[54].

Majority of patients (72.73%) had a disease duration of less than 5 years. None of the enrolled patients had a first or second degree relative with IBD, consistent with low prevalence of positive family history of IBD in India as compared to west. A familial aggregation of IBD has been reported in 8 % to 14 % of patients from the West[55,56]. In an Indian study, a history (definite as well as possible) of IBD in one or more family members was present in approximately 4 % of patients with IBD (CD>UC)[54]. These data suggest that the familial occurrence in Indian patients is less than that reported in the West.

None of the patients had any history of Alcohol, Smoking or Opium abuse, neither did any of them have a history of Intravenous Drug Abuse. All patients had received standard of care treatment for their active disease, 7 patients (21.2%) had received i.v. steroids whereas 29 patients (87.8%) had received oral steroids. 2 patients (6.1%) had exposure to Infliximab and Adalimumab in the past whereas 13 patients (39.39%) were taking Azathioprine which is a standard practice for the treatment of UC.

Patients were followed-up for their response at each session of FMT and the disease activity was assessed by full Mayo Clinic Score and SCCAI. Faecal slurry retention time was noted for all patients. They were encouraged to retain stool slurry for as long as possible. The mean retention time at the first visit was 2.54 ± 1.35 hours, which progressively increased to 4.79 ± 1.02 hours at the 4th visit and remained high around 4.81 ± 0.73 hours at the 7th visit. The number of patients able to retain the slurry for at least 4 hours at the 1st visit was 11/33 (33.3%) which increased to 96.29% (26/27) patients at the 7th visit. The acceptability and tolerability of the procedure kept on improving with each visit.

Patients in our study were recruited while being on Immunomodulators and steroids and FMT was added by a multi-session protocol. The objective of our study was to assess the response to the multiple sessions of FMT by means of the Mayo Score and SCCAI. The mean total Mayo score at visit 1 was 7.21 ± 1.96 which improved over the next sessions to 2.11 ± 1.48 at visit 5 and remained at 2.07 ± 1.59 at visit 7. The above results when plotted on a trendline had an R^2 value of 0.9743. Further analysis of the trend of the mean Mayo score was done using then Mann-Kendall test revealed a Kendall Coefficient value of 0.707 with a p value of <0.01 suggesting a significant downward trend in the mean Mayo score across multiple visits. On a per protocol analysis, the proportion of patients achieving Clinical remission was 39.3% (11/28) at visit 3, 63% (17/27) at visit 4 and 77.8% (21/27) at the end of our protocol. The proportion of patients achieving Endoscopic Remission was 70.4% at visit 4 and 81.5% at visit 7. The proportion of patients achieving Clinical remission in the previous RCTs ranged from 24-50%[39-42]. The higher proportion of patients with Clinical remission in our study may be due to the use of multisession FMT over a period of 22 weeks through the colonoscopy route as well as use of single healthy donor.

The 4 RCTs varied in terms of the FMT infusion protocol, especially the route of administration and frequency of infusions. Moayyedi et al. administered weekly FMT or placebo enemas for 6 weeks. Rossen et al administered FMT or placebo (autologous stool) via a nasoduodenal tube at time zero and 3 weeks. Costello et al administered 2 enemas at week 7 following a baseline colonoscopy at week 0. Paramsothy et al. were more aggressive, administering FMT or placebo by colonoscopy at time zero and via enemas 5 times per week for 8 weeks. The donors used in these RCTs were also different from the present study ranging from unrelated healthy donors, pooled donors or spouse and relatives[39-42]. RCTs with a rectal or a colonic route had a better response rates as compared to the Upper GI route. In a meta-analysis based on cohort studies, the pooled proportion of clinical remission rates with upper and lower GI tract administration of faecal slurry were 8% and 31%, respectively[46]. Also, Instillation of the faecal slurry in the upper GI tract may not be effective as it has been hypothesized that gastric acid can destroy Bacteroides and Firmicutes. As inflammation in UC starts in rectum and proceeds proximally, and dysbiosis is expected to be more in inflamed areas than the noninflamed ones, so Colonoscopic route of instillation was chosen in this study. Unlike administration into upper GI tract, there was also no risk of aspiration in colonoscopic route. Assessment of Clinical response on a per protocol analysis revealed that 18 patients (56.3%) achieved clinical response at the 2nd visit, 7 patients (25%) at the 3rd visit and 6 patients (22.2%) achieved it at the 4th visit.

SCCAI scores were noted at each visit. The mean SCCAI score at the 1st visit were 7.21 ± 2.52, they improved over the course of the next visits to 1.37± 1.57 at the 4th visit and 0.96 ± 1.93 at the 7th visit. On a per protocol analysis, SCCAI scores of < 1 were achieved in 10/28 (35.7%), 16.27 (59.3%), and 21/27(77.8%) patients at 3rd, 4th, and 7th visits respectively. The SCCAI trend with each visit of FMT was analysed using Mann Kendall test which revealed a significant positive

association of the SCCAI with increasing FMT sessions with a Kendall coefficient value of 0.716 and p value of <0.01.

There is no specific protocol as to the number of FMT sessions to be conducted and the interval between two FMT sessions. Microbial engraftment in patients with rCDI has been demonstrated to increase from days 2 to 6 after FMT and it plateaus by days 28 to 45. This engraftment is typically sustained for months[57]. However UC has diverse etiopathogenesis with a persistent state of dysbiosis and hence multiple sessions of FMT may be required for sustained benefit[35]. Increasing the application frequency and prolonging the treatment time of FMT applications can achieve a better clinical remission[58]. Other studies have also postulated that one-time or short-term repeated FMT may result in failure of the clinical treatment. For the long-term and the sustainable change of gut microorganisms, repeated treatments over a few weeks are necessary[59].

Considering the above, our study has tried to elucidate the number of FMT sessions to be administered to a patient of Ulcerative colitis. The Kendall Coefficient score has progressively declined for the groups of visits 1-4, visits 1-5, visits 1-6 and visits 1-7. This, combined with the post HOC analysis of the trend of Mayo score over the seven visits, indicates that the benefit in Mayo score after the 4th visit of FMT may not be statistically significant.

FMT was combined with standard of care IBD therapy. This approach allowed these therapies to work synergistically. Remodelling the intestinal microbiota by FMT in all likelihood also improved the patient's response to other therapies. None of the patients had significant adverse event after FMT. The most common visits were Bloating, pain abdomen and Flatulence on the day of procedure. None of the patients had to be hospitalised for the adverse events.

Our study had a few limitations. There was no control group to compare the efficacy of FMT. The sample size was small. We could not analyse

the gut microbiome of the patients before and after FMT due to logistical reasons.

SUMMARY AND CONCLUSION

FMT for UC is a novel and emerging therapy, still not a part of the standard of care of its treatment. This was an interventional, prospective and uncontrolled study in patients with Active UC. The patients received standard of care treatment along with 7 cycles of FMT over 22 weeks. 33 patients were enrolled initially, however 6 patients were lost to follow up. Patients were followed-up for their clinical response at each FMT session and the disease activity was assessed by full Mayo Clinic Score and SCCAI.

The mean retention time and the tolerability and acceptability of the procedure increased over time.

On a per protocol analysis, the proportion of patients achieving Clinical remission was 39.3% at visit 3, 63% at visit 4 and 77.8% at the end of our protocol. 18 patients (56.3%) achieved clinical response at the 2nd visit, a further 7 patients (25%) at the 3rd visit and the rest 6 patients (22.2%) achieved it at the 4th visit. The proportion of patients achieving Endoscopic remission was 37.5% at the second visit, increased to 70.4% at visit 4 and 81.5% at visit 7.

The mean total Mayo score improved significantly over the 7 sessions. Further analysis of the trend of the mean Mayo score was done using then Mann-Kendall test suggested a significant downward trend in the mean Mayo score across multiple visits. However, post Hoc analysis and the Kendall Coefficient scores at different visits suggested that the benefit in the total Mayo score after the 4th cycle was not statistically significant.

The mean SCCAI score also improved significantly over the course of the 7 sessions. Analysis using the Mann- Kendall test here too suggested a significant downward trend in the mean SCCAI.

None of the patients had significant adverse event after FMT. The most common visits were Bloating, pain abdomen and Flatulence on the day of procedure. None of the patients had to be hospitalised for the adverse events.

Intensive dosing, multidonor, faecal microbiota transplantation induces clinical remission and endoscopic improvement in active ulcerative colitis. However, the standardisation of treatment of FMT pertaining to the route of administration, the number of sessions of FMT and the optimal time interval between sessions needs further dedicated studies.

CONCLUSION:

FMT is a novel treatment addition to the current armamentarium available for the management of Ulcerative Colitis. In our study, intensive multisession FMT has demonstrated a significant reduction in the disease activity. However, further research is required to delineate the exact protocol to be employed with respect to the number of sessions, route of administration, patient and donor selection.

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S.No.	PT NAME	Age	Sex	Disease Duration	Family history of	Addictions	Co-morbidities	Previous Biologicals	Exposure to Immunomodulators	Oral steroids	i.v. Steroids	Appendicectomy	Addictions	BMI	hsCRP	Retention time							Number of stools								
																Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 1	Visit 2
1	KK	33	F	0.5	NO	NO	HYPOTHYROIDISM	YES	AZT 25 mg	Y	N	NO	NO	20.1	103	0.3	0.45	3	3	3	4	5	2	2	2	2	0	0	0	1	1
2	SK	42	F	1	NO	NO	NO	NO	N	Y	Y	NO	NO	22.4	68	4	5	4	5	5	5	6	2	2	1	0	0	0	0	1	0
3	AS	36	M	7	NO	NO	NO	NO	N	Y	N	NO	NO	22.5	46	4	5	4	5	5	5	5	1	2	1	1	0	0	0	0	0
4	CS	25	M	0.1	NO	NO	NO	NO	N	Y	N	NO	NO	21.4	86	2	1	4	6	6	6	5	2	2	2	1	2	1	0	1	0
5	VS	25	M	0.3	NO	NO	NO	NO	N	Y	N	NO	NO	20.5	34	2	2	5	-	-	-	-	2	0	0	-	-	-	-	0	0
6	SK	42	F	-	NO	NO	NO	NO	N	Y	N	NO	NO	23.5	126	2	4	-	-	-	-	-	3	2	-	-	-	-	-	2	1
7	SS	16	M	1	NO	NO	NO	YES	N	Y	Y	NO	NO	22.9	42	0.3	1	-	-	-	-	-	1	1	-	-	-	-	-	0	0
8	KK	29	F	0.4	NO	NO	NO	NO	N	Y	N	NO	NO	19.3	28	3	4	5	6	6	5	5	2	0	0	0	0	0	0	0	0
9	SL	30	F	1	NO	NO	NO	NO	AZT 100mg	Y	N	NO	NO	20.4	75	3	3	4	5	5	5	5	3	2	1	0	0	0	0	1	0
10	M	34	F	6	NO	NO	NO	NO	AZT 100mg	Y	N	NO	NO	23.5	54	4	4	5.3	5	5	6	5	2	2	0	2	1	0	0	1	0
11	NM	29	F	48	NO	NO	NO	NO	N	Y	N	NO	NO	21.3	88	4	4	4	4	3	5	5	3	3	2	2	0	0	0	1	1
12	SS	45	M	0.6	NO	NO	NO	NO	AZT 100mg	Y	N	NO	NO	24.3	106	1	1	-	-	-	-	-	3	2	-	-	-	-	-	1	0
13	MK	27	F	0.1	NO	NO	NO	NO	N	Y	N	NO	NO	20.5	76	5	5	3	4	5	5	5	3	1	1	0	0	1	1	1	0
14	A	55	F	9	NO	NO	NO	NO	N	N	N	NO	NO	19.4	49	2	3	5	5	0.3	5	5	2	2	1	0	0	0	0	0	0
15	MR	40	M	17	NO	NO	NO	NO	AZT 100mg	N	N	NO	NO	21.9	35	4	4	6	5	5	1	4	3	2	1	0	0	0	0	0	0
16	JS	33	M	2	NO	NO	NO	NO	AZT 50mg	Y	Y	NO	NO	22.4	72	1	3	5	5	6	6	5	3	1	0	0	0	0	0	1	0
17	Z	20	F	2	NO	NO	NO	NO	N	Y	N	NO	NO	25.3	51	2	3	4	4	5	5	6	2	0	0	0	0	0	0	1	0
18	NM	26	F	5	NO	NO	NO	NO	AZT 100mg	N	N	NO	NO	19.6	18	1	2	5	7	5	5	4.3	2	0	0	0	0	0	0	0	0
19	BK	28	F	2	NO	NO	NO	NO	AZT 75mg	Y	N	NO	NO	28.6	23	3	4	4	5	5	4	4.5	1	1	0	0	0	0	0	0	0
20	HS	31	F	2	NO	NO	NO	NO	N	Y	N	NO	NO	19.5	97	2	4	4	4	5	4	5	2	2	1	2	2	2	2	2	1
21	GS	20	M	1	NO	NO	NO	NO	AZT 100mg	Y	N	NO	NO	20.1	71	1	2	6	6	6	6	5	1	1	0	0	0	0	0	1	0
22	US	27	F	5	NO	NO	NO	NO	N	Y	N	NO	NO	21.4	14	3	5	5.3	5.3	4	5	5	2	0	0	0	0	0	0	0	0
23	BK	32	F	2	NO	NO	CELIAC DISEASEE	NO	N	Y	N	NO	NO	22.1	54	2	4	4	5	6	6	5	3	2	0	0	0	1	1	1	0
24	RG	37	F	13	NO	NO	NO	NO	AZT 25 mg	Y	N	NO	NO	22.8	116	4	4.15	4	6	4.5	5	5	3	1	0	0	0	0	0	2	0
25	PK	25	M	3	NO	NO	NO	NO	N	Y	Y	NO	NO	18.1	42	0.2	1.3	3	4	4	2.3	4	1	1	1	1	1	0	0	1	0
26	PK	11	M	0.5	NO	NO	NO	NO	N	Y	Y	NO	NO	19.2	82	4	3.5	3.3	2	3	3	4	2	1	2	1	2	1	1	2	0
27	SS	50	F	0.5	NO	NO	NO	NO	N	Y	N	NO	NO	27.3	32	2	4	5	5	5	5	2	1	2	0	1	0	0	1	1	0
28	MK	30	F	3	NO	NO	NO	NO	N	Y	N	NO	NO	22.9	43	3	5	1	4	4	4	5	2	1	2	1	2	2	0	1	1
29	GS	32	M	-	NO	NO	NO	NO	AZT 100mg	Y	N	NO	NO	20.1	23	1	3	4	4	4	4	5	1	2	1	0	0	0	2	1	0
30	GD	60	F	1.9	NO	NO	BA	NO	N	Y	Y	NO	NO	26.3	54	2	4	-	-	-	-	-	2	0	-	-	-	-	-	1	0
31	V	23	M	5	NO	NO	NO	NO	AZT 25 mg	Y	Y	NO	NO	22.5	15	4	5	6	5	5	5	5	2	1	0	0	0	0	0	0	0
32	RK	42	M	0.1	NO	NO	NO	NO	N	N	N	NO	NO	20.2	5	4	-	-	-	-	-	-	1	-	-	-	-	-	-	0	-
33	AK	27	M	8	NO	NO	NO	NO	AZT 100mg	Y	N	NO	NO	22.9	46	4	5	5	5	4	5	5	2	1	1	0	0	0	0	1	0

S.No.	PT NAME	Blood in stools					Endoscopic Mayo score							Physician global assesment							Total Mayo score							Disease extent						
		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
1	KK	0	0	0	0	0	3	3	2	1	0	0	0	2	2	2	1	1	1	1	8	8	6	4	1	1	1	E3	E3	E3	E3	ER	ER	ER
2	SK	0	0	0	0	0	2	2	2	1	1	1	1	2	1	1	1	1	1	1	7	5	4	2	2	2	2	E1	E1	E2	E1	E1	E1	E1
3	AS	0	0	0	0	0	3	2	2	1	2	2	1	1	1	1	1	1	1	1	5	5	4	3	3	3	2	E1	E1	E1	E1	E1	E1	E1
4	CS	0	0	0	0	0	3	2	2	2	2	1	1	2	1	1	1	1	1	1	8	5	5	4	5	3	2	E3	E2	E2	E2	E2	E2	E2
5	VS	0	-	-	-	-	2	0	0	-	-	-	-	1	1	-	-	-	-	-	5	1	1	-	-	-	-	E1	ER	ER	-	-	-	-
6	SK	-	-	-	-	-	3	3	-	-	-	-	-	3	2	-	-	-	-	-	11	8	-	-	-	-	-	E3	E3	-	-	-	-	-
7	SS	-	-	-	-	-	3	2	-	-	-	-	-	1	1	-	-	-	-	-	5	4	-	-	-	-	-	E3	E3	-	-	-	-	-
8	KK	0	0	0	0	0	2	0	0	0	0	0	0	1	1	1	1	1	1	0	5	1	1	1	1	1	1	E2	ER	ER	ER	ER	ER	ER
9	SL	0	0	0	0	0	3	1	1	0	0	0	0	2	1	1	1	1	1	1	9	4	3	1	1	1	1	E2	E2	E2	ER	ER	ER	ER
10	M	0	0	0	0	0	2	2	1	2	2	1	1	2	2	1	1	1	1	1	7	6	2	5	4	2	2	E1	E1	E1	E1	E1	E1	E1
11	NM	0	0	0	0	0	3	3	3	3	2	1	1	2	2	1	1	1	1	1	9	9	6	6	3	2	2	E2	E2	E2	E2	E2	E2	E2
12	SS	-	-	-	-	-	3	3	-	-	-	-	-	2	1	-	-	-	-	-	9	6	-	-	-	-	-	E2	E2	-	-	-	-	-
13	MK	0	0	0	0	0	3	3	2	1	0	2	1	2	1	1	1	1	1	1	9	5	4	2	1	4	3	E3	E3	E2	E2	ER	E2	E2
14	A	0	0	0	0	0	2	2	2	1	1	1	0	2	1	1	1	1	1	1	6	5	4	2	2	2	1	E1	E1	E1	E1	E1	E1	ER
15	MR	0	0	0	0	0	1	1	2	2	1	1	0	2	1	1	1	1	1	1	6	4	4	3	2	2	1	E2	E2	E2	E2	E1	E1	ER
16	JS	0	0	0	0	0	3	1	1	0	0	0	0	2	1	1	1	1	1	1	9	3	2	1	1	1	1	E3	-	E3	ER	ER	ER	ER
17	Z	0	0	0	0	0	3	2	1	1	0	0	0	1	1	1	1	1	1	1	7	3	2	2	1	1	1	EE2	E2	E2	E2	ER	ER	ER
18	NM	0	0	0	0	0	2	2	2	0	0	1	1	1	1	1	1	1	1	1	5	3	3	1	1	2	2	E2	E2	E2	ER	ER	E2	E2
19	BK	0	0	0	0	0	3	1	1	1	1	1	0	1	1	1	1	1	1	1	5	3	2	2	2	2	1	E1	E1	E1	E1	E2	E2	ER
20	HS	0	0	0	0	0	3	3	3	3	2	2	2	3	2	2	2	2	2	1	10	8	6	7	6	6	5	E2	E2	E2	E2	E2	E2	E2
21	GS	0	0	0	0	0	3	3	2	2	1	1	0	2	2	1	1	1	1	1	7	6	3	3	2	2	1	E2	E2	E2	E2	E2	E2	ER
22	US	0	0	0	0	0	2	0	0	0	0	0	0	1	1	1	1	1	1	1	5	1	1	1	1	1	1	E3	ER	ER	ER	ER	ER	ER
23	BK	0	0	0	1	0	1	1	0	0	0	3	2	2	1	1	1	1	2	1	7	4	1	1	1	7	4	E2	E2	ER	ER	ER	E2	E2
24	RG	0	0	0	0	0	3	3	1	1	1	0	0	3	2	1	1	1	1	1	11	6	2	2	2	1	1	E2	E2	E2	E2	E2	ER	ER
25	PK	0	0	0	0	0	3	1	1	0	0	1	0	2	1	1	1	1	1	1	7	3	3	2	2	2	1	E2	E2	E2	ER	ER	E2	ER
26	PK	0	0	0	0	0	3	2	3	3	2	2	2	3	1	2	2	1	1	1	10	4	7	6	5	4	4	E3	E3	E3	E3	E3	E3	E3
27	SS	0	0	0	0	1	3	0	1	0	0	0	3	2	1	1	1	1	1	2	7	3	2	2	1	1	7	E2	ER	E2	ER	ER	ER	E2
28	MK	0	0	0	0	0	3	3	2	2	1	2	1	2	2	2	1	1	2	1	8	7	6	4	4	6	2	E2	E2	E2	E2	E2	E2	E2
29	GS	0	0	0	0	0	3	2	1	0	0	0	2	2	1	1	1	1	1	1	7	5	3	1	1	1	5	E2	E2	E2	ER	ER	ER	E2
30	GD	-	-	-	-	-	3	1	-	-	-	-	-	2	1	-	-	-	-	-	8	2	-	-	-	-	-	E2	E1	-	-	-	-	-
31	V	0	0	0	0	0	2	0	1	0	0	0	0	1	1	1	1	1	1	1	5	2	2	1	1	1	1	E1	ER	E1	ER	ER	ER	ER
32	RK	-	-	-	-	-	2	-	-	-	-	-	-	1	-	-	-	-	-	-	4	-	-	-	-	-	-	E1	-	-	-	-	-	-
33	AK	0	0	0	0	0	3	2	3	1	0	0	0	2	1	1	1	1	1	1	8	4	5	2	1	1	1	E2	E2	E3	E3	ER	ER	ER

		UCEIS							SCCAI							ADVERSE EFFECTS						
S.No.	PT NAME	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
1	KK	6	6	4	2	0	0	0	9	6	3	2	1	0	0	BORBORYGMI	PAIN ABDOMEN	NIL	MYOPATHY	BORBORYGMI,PAIN ABDOMEN	FLATULENCE	NIL
2	SK	4	3	3	2	2	2	2	8	3	3	1	0	0	0	PAIN ABDOMEN	NIL	MENORRHAGIA	MENORRAGIA	BORBORYGMI	BORBORYGMI	NIL
3	AS	6	3	3	2	4	3	2	3	2	1	1	0	0	0	BORBORYGMI	FLATULENCE	BORBORYGMI	NIL	BORBORYGMI	BORBORYGMI	NIL
4	CS	5	3	3	3	3	2	2	9	3	2	2	5	2	0	BORBORYGMI	BORBORYGMI	BORBORYGMI	NIL	NIL	NIL	NIL
5	VS	3	0	0	-	-	-	-	5	2	0	-	-	-	-	FLATULENCE	FLATULENCE	FLATULENCE	-	-	-	-
6	SK	5	5	-	-	-	-	-	10	7	-	-	-	-	-	PAIN ABDOMEN	FLATULENCE	-	-	-	-	-
7	SS	6	3	-	-	-	-	-	5	2	-	-	-	-	-	FLATULENCE	FLATULENCE	-	-	-	-	-
8	KK	3	0	0	0	0	0	0	5	2	1	0	0	0	0	BORBORYGMI	BORBORYGMI	FLATULENCE	FLATULENCE	NIL	NIL	NIL
9	SL	5	2	2	0	0	0	0	8	4	2	0	0	0	0	FLATULENCE	BORBORYGMI	BORBORYGMI	NIL	NIL	NIL	BORBORYGMI
10	M	3	4	1	3	4	2	2	7	5	2	4	3	0	0	FLATULENCE	PAIN ABDOMEN	RECTAL PAIN	RECTAL PAIN	FLATULENCE	NIL	NIL
11	NM	6	5	4	4	3	2	2	12	10	5	3	2	0	0	PAIN ABDOMEN	PAIN ABDOMEN	PAIN ABDOMEN	PAIN ABDOEMN	BORBORYGMI	NIL	NIL
12	SS	6	5	-	-	-	-	-	11	5	-	-	-	-	-	PAIN ABDOMEN	BORBORYGMI	-	-	-	-	-
13	MK	5	5	3	2	0	3	2	9	3	2	1	0	2	2	PAIN ABDOMEN	FLATULENCE	FLATULENCE	FLATULENCE	NONE	BORBORYGMI	BORBORYGMI
14	A	4	3	3	2	2	1	0	6	5	2	2	2	1	0	PAIN ABDOMEN,BORBORYGMI	BORBORYGMI	WORSENING OF DIARROEA	NIL	FLATULENCE, BLOATING	NIL	NIL
15	MR	2	2	2	2	2	2	0	6	5	2	1	0	0	0	PAIN ABDOMEN	PAIN ABDOMEN	FLATULENCE	BLOATING	BLOATING	NIL	NIL
16	JS	5	2	1	0	0	0	0	8	2	1	0	0	0	0	BLOATING	BLOATING	BORBORYGMI	NIL	NIL	NIL	NIL
17	Z	5	3	2	1	0	0	0	6	1	0	0	0	0	0	PAIN ABDOMEN	FLATULENCE	FLATULENCE	BLOATING	FLATULENCE,BLOATING	NIL	NIL
18	NM	3	3	3	0	0	1	2	6	3	2	0	0	0	0	FLATULENCE	FLATULENCE	BORBORYGMI	NIL	NIL	BORBORYGMI	FLATULENCCE
19	BK	6	2	2	1	1	1	0	3	2	0	0	0	0	0	PAIN ABDOMEN	BORBORYGMI	FLATULENCE	FLATULENCE	NIL	FLATULENCE	NIL
20	HS	5	5	5	4	3	3	2	11	6	4	6	5	5	5	BORBORYGMI	BORBORYGMI	BORBORYGMI	FLATULENCE ,PAIN ABDOMEN	PAIN ABDOMEN, BLOATING	NIL	FLATULENCE
21	GS	5	5	3	2	2	1	0	6	3	2	2	1	0	0	PAIN ABDOMEN	FLATULENCE	FLATULENCE	FLATULENCE	FLATULENCE	BORBORYGMI	NIL
22	US	4	0	0	0	0	0	0	5	1	0	0	0	0	0	PAIN ABDOMEN	NIL	BORBORYGMI	BLOATING	BLOATING	RECTAL PAIIN	NIL
23	BK	2	1	0	0	0	5	3	9	6	2	1	0	7	3	BORBORYGMI	BORBORYGMI	RECTAL PAIN	BLOATING	BLOATING	NIL	NIL
24	RG	5	5	2	1	1	0	0	10	4	1	0	0	0	0	BORBORYGMI,FLATULENCE	FLATULENCE	FLATULENCE	BLOATING	BORBORYGMI	NIL	NIL
25	PK	5	2	2	0	0	2	0	7	5	2	2	2	0	0	RECTAL IRRITATION	PAIN ABDOMEN	FLATULENCE	BLOATING	BLOATING	NIL	FLATULENCE
26	PK	6	4	5	6	4	3	3	10	3	5	3	4	4	3	PERANAL PAIN IRRITATION	FLATULENCE	PAIN ABDOMEN	BLOATING	BORBORYGMI	NIL	NIL
27	SS	5	0	2	0	0	0	5	6	2	0	2	0	0	7	PAIN ABDOMEN	FLATULENCE	NIL	BORBORYGMI	NIL	BLOATING	BORBORYGMI
28	MK	5	5	4	3	2	3	2	10	5	5	4	4	3	1	BORBORYGMI	BORBORYGMMI	BORBORYGMI	FLATULENCE	PAIN ABODMEN,BORBORYGMI	FLATULENCE	FLATULENCE
29	GS	5	4	1	0	0	0	4	6	5	2	0	0	0	5	PAIN ABDOMEN	FLATULENCE	FLATULENCE	NIL	NIL	NIL	NIL
30	GD	5	2	-	-	-	-	-	8	2	-	-	-	-	-	BLOATING	BLOATING	-	-	-	-	-
31	V	3	0	2	0	0	0	0	6	2	0	0	0	0	0	BORBORYGMI	BORBORYGMI	BORBORYGMI	BORBORYGMI	BORBORYGMI	NIL	FLATULENCE
32	RK	3	-	-	-	-	-	-	1	-	-	-	-	-	-	NIL	-	-	-	-	-	-
33	AK	5	4	5	2	0	0	0	7	2	2	0	0	0	0	BORBORYGMI	BORBORYGMI	FLATULENCE	HAIR FALL	BORBORYGMI	NIL	NIL

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The Principal,
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Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.05.2019 has approved the plan of thesis of **Dr. Halgale Tanveer Jakirhusain**, a student of your college for **DM Medical Gastroenterology** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

Pattern of response to fecal microbiota transplantation in patients with active ulcerative colitis

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The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

S P Singh

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

PATTERN OF RESPONSE TO FECAL MICROBIOTA TRANSPLANTATION IN PATIENTS WITH ACTIVE ULCERATIVE COLITIS

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

IN

GASTROENTEROLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

FEBURARY, 2019

DR. HALGALE TANVEER JAKIRHUSAIN

DEPARTMENT OF GASTROENTEROLOGY

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PUNJAB

ABSTRACT OF PLAN OF THESIS

Title	PATTERN OF RESPONSE TO FECAL MICROBIOTA TRANSPLANTATION IN PATIENTS WITH ACTIVE ULCERATIVE COLITIS
For the degree of	D.M. (Gastroenterology)
Name of the candidate	Dr. Halgale Tanveer Jakirhusain
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INTRODUCTION: The role of gut microbiome in health and inflammation has gained international attention in recent times. The success of fecal microbiota transplantation (FMT) in treatment of *Clostridium difficile* infection led to the hypothesis that it may play an important role in Inflammatory Bowel Disease (IBD) as well. Randomized controlled trials have demonstrated efficacy of FMT in induction of remission in mild-moderate Ulcerative Colitis (UC). However there is paucity of data which looks into the pattern of response to FMT, its optimal timing and optimal dosing frequency.This study aims to study the pattern of response to FMT in patients with Active Ulcerative colitis. Patients will receive retention enemas or through colonoscopy and will be looked for remission/response at every visit.

Aim of Study: To study the Pattern of response of FMT in patients with Active Ulcerative Colitis.

Materials & methods: Interventional, prospective and uncontrolled study which will be conducted on patients attending the outpatient department or admitted in Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, India.

Clinical Significance: Sessions of FMT required for clinical response/remission in patients with Active Ulcerative Colitis

Keywords: FMT: Fecal Microbiota Transplantation, UC: Ulcerative Colitis

(Signature) Candidate

(Signature) Co-supervisor

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(Signature) Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"PATTERN OF RESPONSE TO FECAL MICROBIOTA TRANSPLANTATION IN PATIENTS WITH ACTIVE ULCERATIVE COLITIS"** exist in the Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate himself/herself under our supervision and guidance.

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APPROVAL PROFORMA
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1. HOD Pharmacology	1. HOD Physiology
2. HOD Surgery	2. HOD Pathology
3. HOD Pathology	3. HOD Pharmacology
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5. Dean Academics	5. HOD Medicine
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Approved: Yes / No

Chairperson
Research Committee

Chairperson
Research Committee

Approved: Yes / No

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Ethics Committee

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BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

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2	**NAME OF THE INSTITUTE**	DAYANAND MEDICAL COLLEGE AND HOSPITAL, TAGORE NAGAR CIVIL LINES, LUDHIANA
3	**COURSE OF STUDY AND SUBJECT**	DOCTORATE IN MEDICINE (D.M.) GASTROENTEROLOGY
4	**DATE OF ADMISSION OF COURSE**	27st AUGUST 2018
5	**TITLE OF THE TOPIC**	PATTERN OF RESPONSE TO FECAL MICROBIOTA TRANSPLANTATION IN PATIENTS WITH ACTIVE ULCERATIVE COLITIS

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Inflammatory bowel disease (IBD) is a relapsing disorder characterised by chronic inflammation of the gastrointestinal tract, and of colon in particular. Although the precise cause of IBD remains unknown, the most accepted hypothesis of IBD pathogenesis to date is that an aberrant immune response against the gut microbiota is triggered by environmental factors in a genetically susceptible host.[1] More than 90 % of the human gut microbiota is composed of four major phyla. The Firmicutes (49–76 %) and Bacteroidetes (16–23 %) phyla dominate, followed to a much less extent by the Proteobacteria and Actinobacteria phyla.[2] Most studies have shown reduced diversity of the gut microbiota in IBD patients. The most consistent observations of altered composition of the gut microbiota in IBD patients are a reduction in Firmicutes and an increase in Proteobacteria.[1] Although these changes in the gut microbiome may be a result of increased inflammation, evidence suggests that it is more likely that the alteration in microbiota are involved in pathogenesis, either due to intolerance to a specific group of commensals or due to an imbalance between the protective and harmful members of the population.[3]

Fecal microbiota transplantation (FMT) is a technique in which intestinal microbiota are transferred from a healthy donor to the patient, with the goal of introducing or restoring a stable microbial community in the gut. Fecal microbiota transplantation has long been used to treat recurrent *Clostridium difficile* infection (CDI) presenting great effectiveness and significant safeness, with cure rates reaching 90%.[4] One of the main mechanisms proposed to

explain the ability of FMT to treat CDI is attributed to its capacity to restore intestinal microbial balance.[5]

Current medical treatment of IBD remains imperfect and a significant number of patients need colectomy to manage their disease. There have been advances in the medical therapy, but these have not translated into appreciable clinical success. Moreover the focus of drug development has been on altering the immune response rather than targeting the factors which lead to activation of the abnormal immune response. FMT has emerged as a novel approach which targets the pathophysiology of IBD i.e. alteration in gut microbiome.

Several studies have evaluated the role of FMT in Ulcerative colitis with studies utilizing different protocols and FMT schedules. In a study conducted by Sood et al, Fecal samples from random unrelated donors were administered through colonoscopy at weeks 0, 2, 6, 10, 14, 18, and 22.[6] Mahajan et al also used a similar study pattern utilising 7 cycles of FMT at weeks 0, 2, 6, 10, 14, 18, and 22 for maintenance of clinical remission in Ulcerative colitis.[7] In a study conducted by Moayyedi et al, patients underwent FMT once weekly for 6 weeks.[8] This study intends to asses the patterns of response to FMT in patients with Active Ulcerative Colitis..

6.2 REVIEW OF LITERATURE

In recent years, there has been considerable progress in our understanding of the gastrointestinal microbiota with consortiums such as the Human Microbiome Project and the European based Metagenomics of the human intestinal tract. Despite the great distribution of microorganisms in different sites of the human body, the most diverse microbial species is found in the gastrointestinal tract (GIT). These commensal and symbiotic communities of microorganisms, also known as microbiota, are able to directly or indirectly influence local and systemic physiology of the human body, including but not limited to the immunologic, endocrine, and nervous systems.[9] Thus, it is reasonable to assume the great impact that perturbations in the complex bidirectional relationship between vertebrate hosts and gut microbes may have on host physiology. Further, this complex interaction can also lead to the onset and maintenance of several diseases, including IBD.[10]

With the deep research into the interaction of gut microbiota and host, probiotics, prebiotics and symbiotics began to be used in UC patients to promote intestinal microbiota homeostasis. Some randomized controlled trials (RCTs) and cohort studies of *Lactobacillus* or VSL#3 have already showed their effect on maintaining UC remission and preventing recurrence.[11,12]

The first use of feces as a pharmacological agent was described in the 4th century by a Chinese medical scientist Ge Hong who advised to consume fresh stool from a healthy neighbor when suffering from severe diarrhea.[13] The first account of FMT in medical literature was reported by Eiseman et al in 1958, when they successfully treated four patients with antibiotic-associated diarrhea with fecal enemas.[14]

FMT has gained interest as a novel therapeutic option for IBD. The first case report of FMT for UC was published in January 1989 by Bennet and Brinkman[15] Subsequently there were reports of FMT for IBD by Borody *et al.* where they reported a durable clinical and histological care.[16] Then, in 2003, a case report documented the complete clinical, colonoscopic and histological reversal in 6 patients of severe relapsing Ulcerative Colitis.[17] With these anecdotal reports and small case series, excitement around the possibility of FMT as a therapy for IBD has grown rapidly

Recent randomized controlled trials (RCTs) for the application of FMT in IBD have focused on UC, which might be simpler in terms of objective clinical metrics, compared with CD.[18] Four high quality RCTs suggesting the efficacy of FMT in active UC patients have been published from different countries [19-22] and a recent systematic review and meta analysis of these studies with 277 participants found that FMT was associated with higher rates of clinical and endoscopic remission compared with placebo.[23] Although these RCTs have significant heterogeneity with different methods of stool preparation, routes of administration, doses, and selection and preparation of the patient, RCTs and meta-analysis suggest that short-term use of FMT might be beneficial for clinical and endoscopic improvement in mild to moderate UC patients.[24]

In a multicentre, double-blind, randomised, placebo-controlled trial conducted by Paramsothy et al.[22] in Australia, patients with Active Ulcerative colitis were randomised to either faecal microbiota transplantation or placebo colonoscopic infusion, followed by enemas 5 days per week for 8 weeks with a primary outcome of steroid-free clinical remission with endoscopic remission

or response (Mayo score ≤2, all subscores ≤1, and ≥1 point reduction in endoscopy subscore) at week 8. The primary outcome was achieved in 27% of patients allocated faecal microbiota transplantation versus 8% who were assigned placebo (risk ratio 3·6, 95% CI 1·1-11·9; p=0·021).

In the other study reported by Rossen et al, 50 patients, with mild to moderately active UC, were treated with either donor stool or autologous FMT (infusion of their own stool as placebo) delivered via naso-duodenal tube at baseline and again 3 weeks later. Only 37 completed assessments for clinical remission combined with a 1-point decrease in the Mayo endoscopic score at week 12. There was no difference in clinical and endoscopic remission between the 2 groups.[20]

In another study conducted by Moayyedi et al [19], 75 patients were randomly assigned to groups that received FMT (50 mL, via enema, from healthy anonymous donors; n = 38) or placebo (50 mL water enema; n = 37) once weekly for 6 weeks. Nine patients who received FMT (24%) and 2 who received placebo (5%) were in remission at 7 weeks (a statistically significant difference in risk of 17%; 95% confidence interval, 2%-33%).

Sood et al. published the therapeutic outcomes of multi-session FMT over 22 weeks via colonoscopy, in patients with steroid dependent UC. The study results showed a better outcome compared to the above RCTs. At week 24, steroid-free clinical remission, clinical response, and endoscopic remission was 46.3%, 75.6%, and 63.4% respectively. Better responses might be attributed to the route of administration and dosing frequency.[6]

When FMT entered the medical community, it became a relatively hot therapeutic strategy, bringing with it both promise and controversy. According

to published articles, transient adverse responses after FMT have been reported, including mild fever, abdominal pain, diarrhea, exhaust, flatulence, and fatigue.[20] However, these adverse effects are self-limiting. De Leon et al[25] reported a UC patient quiescent for more than 20 years who developed a flare of UC after FMT.

The 4 RCTs varied in terms of the FMT infusion protocol, especially the route of administration and frequency of infusions. Moayyedi et al. administered weekly FMT or placebo enemas for 6 weeks. Rossen et al administered FMT or placebo (autologous stool) via a nasoduodenal tube at time zero and 3 weeks. Paramsothy et al. were more aggressive, administering FMT or placebo by colonoscopy at time zero and via enemas 5 times per week for 8 weeks. Although the dosing frequency was not very intense in the study by Sood et al., the rate of steroid-free remission was comparable to that from a more intensive FMT protocol.

The above RCTs and meta-analysis suggest that short-term use of FMT might be beneficial for clinical and endoscopic improvement in mild to moderate UC patients. However, before FMT can be recommended as a routine therapeutic practice, further studies are necessary to define the optimal timing, optimal dosing frequency, route of delivery, role of antibiotic preconditioning, and donor selection for each patient, as well as its long-term safety and efficacy.[24]

The incidence of IBD is on the rise in India. With the genetic, environmental and dietary factors playing in the background, optimal management of IBD is a challenge. In a resource limited country like ours, FMT provides an interesting alternative to treat IBD 'naturally'.

6.3 AIMS AND OBJECTIVES

- To study pattern of response to FMT in patients with Active Ulcerative Colitis.

7. MATERIALS AND METHODS

STUDY DESIGN

This study will be conducted on the patients attending the outpatient department or admitted in Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, India.

Consecutive patients suffering from active Ulcerative Colitis attending the outpatient or admitted indoors in Department of Gastroenterology, DMC & H will be enrolled for the study. Patients will be educated about fecal microbiota transplantation (FMT) through a Patient Information Sheet (PIS) which will be provided to each patient.

Consecutive patients suffering from Active Ulcerative Colitis will be enrolled after obtaining informed consent. Donor faeces (200-300 gm) will be diluted in 200-300 ml normal saline. After proper blending, the slurry will be filtered and particulate matter will be removed. The resultant solution will be administered to the patient through colonoscopy, within 6 hours of preparation.

Patient will be encouraged to retain the solution for as long as possible. These FMTs will be done at weeks 0, 2, 6, 10, 14, 18, and 22 (i.e. seven sessions of FMT).

High fiber diet will be advised to stimulate proliferation of infused bacteria. The subjects will be continued on their standard of care pharmacological maintenance regimen with 5-ASA compounds/ immunomodulators.

7.1 SOURCES OF DATA

Consecutive patients suffering from active Ulcerative Colitis attending the outpatient or admitted indoors in Department of Gastroenterology, DMC & H will be enrolled for the study.

7.2 METHODS OF COLLECTION OF DATA

DATA COLLECTION

Confirmed cases of Active Ulcerative Colitis will be enrolled and will receive FMT for 6 months (at weeks 0, 2, 6, 10, 14, 18, and 22). Patients will be followed-up for their clinical response at every visit and the disease activity will be assessed by Simple Clinical Colitis Activity Index (SCCAI). Subjects will be continued on their standard pharmacotherapy.

INCLUSION CRITERIA

- Age ≥18 years
- Confirmed Active Ulcerative Colitis patients
- Able to give informed consent and/or assent as appropriate

EXCLUSION CRITERIA

- Patients in clinical remission
- Patients having toxic megacolon
- Treatment naïve patients
- Pregnant and lactating ladies
- Prior colectomy
- Positive stool test for any of the following: Clostridium difficile, Salmonella, Shigella, Yersinia, Campylobacter, E. coli by standard stool culture.

- Regular probiotic supplement use within prior 4 weeks to enrollment
- Severe immunodeficiency, inherited or acquired (e.g. HIV, chemotherapy, or radiation therapy)
- Patients unwilling or unable to give consent or participate in all study requirements

INCLUSION CRITERIA FOR DONOR

- Age >18 years
- Score of 2,3 or 4 on Bristol stool scale
- Stool culture and microscopy tests negative for common detectable enteric pathogens (Salmonella, Shigella, Campylobacter, Vibrio parahemolyticus, Vibrio cholera, Candida albicans, E. coli, Clostridium difficile, Entamoeba histolytica, Giardia lamblia, Cryptosporidium, Ascaris lumbricoides, Trematodes/tape worms)
- Negative screening for hepatitis A, anti HCV, HBsAg, syphilis and anti HIV within three months of donation.

EXCLUSION CRITERIA FOR DONOR

- Tattoos or body piercings within the last 6 months
- High-risk sexual behaviors
- Communicable illnesses or antibiotic treatment within the past 3 months
- Intrinsic gastrointestinal illnesses such as irritable bowel syndrome, inflammatory bowel disease, gastrointestinal malignancies or major gastrointestinal surgical procedures.
- Ongoing immune-modulator therapy for any concurrent illness
- A history of chronic pain syndromes (fibromyalgia, chronic fatigue) or neurologic, neurodevelopmental disorders

- Metabolic syndrome, obesity (BMI of >30), or moderate-to-severe undernutrition (malnutrition)
- A history of malignant illnesses or ongoing oncologic therapy

PROTOCOL FOR PERFORMING FMT

Donor preparation

- A gentle osmotic laxative will be given the night before procedure
- Donor will be required to avoid of any food to which the recipient may be allergic for 5 days before the procedure
- Donor will be instructed to notify if any symptoms of infection occur between screening and time of donation.
- Stool microbiota composition of the donor will be assessed by 16s RNA method to check the quality of the donor sample.

Recipient preparation

- Large volume bowel preparation a day before the procedure.

PREPARATION OF STOOL AND ADMINISTRATION

- Stool sample will be collected in an airtight container and will be used within 6 hours of collection.
- Universal precautions will be observed while handling the stool.
- Preservative free normal saline will be used to dilute the stool sample
- Using a blender, stool will be homogenized and diluents added till it reaches a liquid consistency.
- Stool will be filtered to remove the particulate matter.
- The finished stool slurry will be used immediately and administered via colonoscope.

DURATION OF STUDY

The study period will start from 1st January 2019 till completion of 7 sessions of the last enrolled patient. Last date for enrollment will be 30th September 2019

OUTCOME

Primary outcome

- To determine the number of FMT sessions needed to achieve clinical remission

Secondary outcome

- To determine the number of FMT sessions needed to achieve clinical response
- To determine the number of FMT sessions needed to achieve Simple Clinical Colitis Activity Index (SCCAI) <1

STATISTICAL ANALYSIS

The clinical response will be assessed at every visit. Multivariate analysis shall be used to find association between the study variable and its correlates. SPSS software shall be used for statistical analysis.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

- Yes, the study requires both investigations and interventions.
- Pre treatment tests include
    - Complete blood counts, Erythrocyte Sedimentation Rate
    - CRP- Quantitative
    - Serum creatinine
    - Random blood sugar
    - Anti HCV antibody, HBs Antigen, Anti HIV antibody
    - Stool routine, Stool culture
    - Stool for Clostridium difficile toxin
    - Cytomegalovirus serology
    - Colonoscopy
    - Histology if available
- The following intervention will be carried out
    - Faecal microbiota solution prepared from donor faeces will be given via colonoscope to the patients after taking an informed consent.

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Yes, Attached along with.

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PROFORMA

SR no. Patient ID Date

CR no. Admn. no Donor ID

Name Age Sex

Address

Contact number

Month and Year of diagnosis

Duration of disease

Family history of IBD: Yes/No (If Yes, specify)

Appendicectomy: Yes/No

Addictions

Smoking No/Occassional/Regular/Heavy

Alcohol No/Occassional/Moderate/Regular

Opium No/Occassional/Regular

IVDU Yes/No

Comorbidity

HTN/T2DM/BA/CAD/COAD/Thyroid disorder/CVA/Malignancy/Psychiatric illness/

Seizures/ Others

BMI

Previous treatments:

	Dose	Duration
IV steroids		
Oral Steroids		

Signature of Candidate **Signature of Supervisor**

5-ASA		
AZA/6MP		
Infliximab		
Adalimumab		
Methotrexate		
Cyclosporine		
Tacrolimus		
Antibiotics		
Salazopyrin		
Budesonide		
Probiotics		
Others		

Indication of FMT:

Mode of FMT:

Signature of Candidate **Signature of Supervisor**

Details of visits:

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
DATE							
Stool quality (Bristol scale)							
Time of collection of sample							
Time of FMT							
Retention time							

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
DATE							
SYMPTOMS							
Number of stools (Mayo score) (A) 0=Normal 1=1-2/day 2=3-4/day 3=>4/day							
Blood in stools Mayo Score (B) 0 = None 1 = Visible blood with stool less than half the time 2 = Visible blood with stool half of the time or more 3 = Passing blood alone							
Nocturnal diarrhea							
Fever							
Pain abdomen							
Fatigue							
Weight loss							
Loss of appetite							
Joint pains							
Others							
INVESTIGATIONS (if available)							
Hb/TLC/Platelets							
ESR							
AST/ALT/ALP							

Signature of Candidate **Signature of Supervisor**

Albumin							
CRP-Quantitative							
Creatinine							
RBS							
HBsAg/Anti HCV/Anti HIV							
Stool R/E							
Stool C/S							
Stool C.diff toxin							
Stool atypical organisms							
Calprotectin (optional)							
CMV serology							
Others							
DISEASE EXTENT							
Proctitis							
Proctosigmoiditis							
Left sided colitis							
Pancolitis							
Backwashileitis							

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
DATE							
COLONOSCOPIC FINDINGS (MAYO SCORE) (C)							
0= Normal or inactive disease							
1= Mild disease (erythema, decreased vascular pattern, mild friability)							
2= Moderate disease (marked erythema, absent vascular pattern, friability, erosions)							
3= Severe disease (spontaneous bleeding, ulceration)							
ADVERSE EVENTS							
Fever							
Pain abdomen							
Nausea							
Vomiting							
Loss of appetite							
Worsening of diarrhea							
Abdominal distension							
Perianal pain							
Flatulence							
Borborygmi							
Bloating							
Rectal pain							

Signature of Candidate **Signature of Supervisor**

Constipation							
UTI							
URI							
LRTI							
CONCOMITANT MEDICATIONS							
Drug 1/Dose							
Drug 2/Dose							
Drug 3/Dose							
PHYSICIAN GLOBAL ASSESSMENT (D)							
Normal (0) Mild (1) Moderate (2) Severe (3)							

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
DATE							
RESPONSE ASSESSMENT							
TOTAL MAYO SCORE (A+B+C+D)							
SIMPLE CLINICAL COLITIS ACTIVITY INDEX							
Bowel frequency (day) 0=1-3 1=4-6 2=7-9 3=>9							
Bowel frequency (night) 1=1-3 2=4-6							
Urgency of defecation 1=Hurry 2=Immediately 3=Incontinence							
Blood in stools 1= Trace 2= Occasionally frank 3= Usually frank							

Signature of Candidate **Signature of Supervisor**

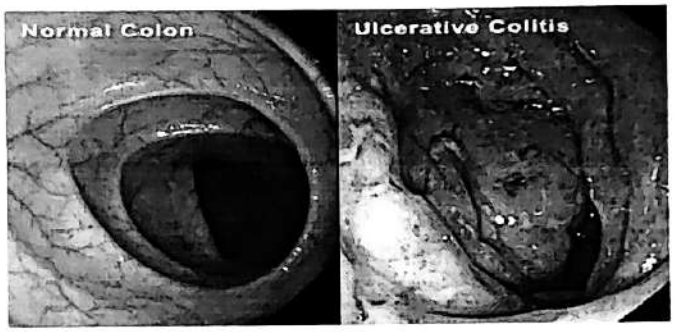
General well being 0= Very Well 1= Slightly Below Par 2=Poor 3=Very Poor 4=Terrible							
Extraintestinal manifestation (1 per manifestation)							
TOTAL							

Signature of Candidate **Signature of Supervisor**

Subject Information Sheet

What is faecal microbiota transplantation (FMT)?

The FMT involves transfer of bacteria from a carefully screened, healthy donor into intestine of patient (recipient) to repopulate the unbalanced gut bacteria. Our body has a lot of necessary bacteria in its gastrointestinal (GI) tract. The idea is to restore the balance of bacteria in the recipient's intestine so that he or she can overcome the disturbed immune system of the body.



Pic 1. Left : Normal colon, Right : Ulcerated colon

How is it performed?

FMT involves a series of infusions of stool from healthy donor blended with saline into patient's colon (large intestine). Medical transfer of stool is undertaken via enema or colonoscopy.

What do I eat before/after FMT?

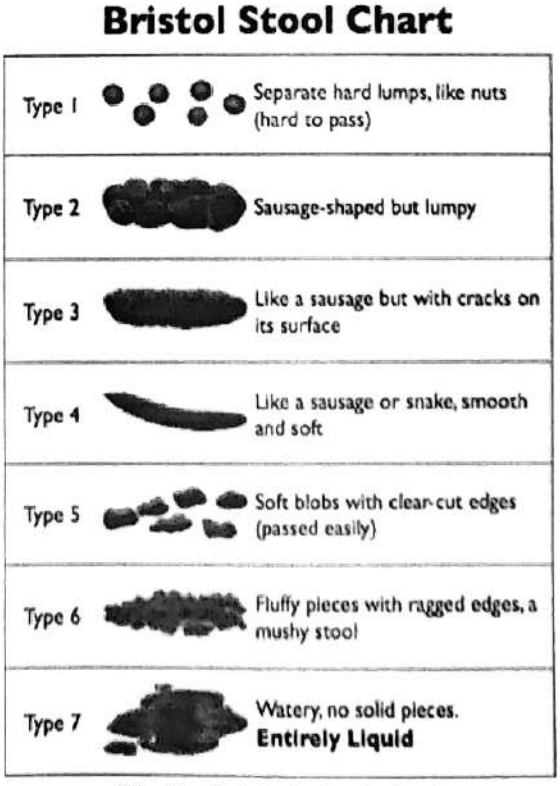
Diet is important to help grow your new flora. Key points to remember:

1. Fibre feeds microbiota so a low fibre diet is important in the two weeks **BEFORE** fecal transplant to starve the bad microbiota.
2. One day prior to FMT, only liquid diet has to be taken.
3. Before FMT, you need to take PEGLEC powder dissolved in water 2-3 times (in the 24 hours preceding FMT), to prepare your large intestine. With this you will experience diarrhea which will recover on its own.
4. A high fibre diet (soluble and insoluble) is important **AFTER** fecal transplant to feed the new microbiota.
5. Eat healthy unprocessed food. Minimise gut stressors like processed foods, gluten, sugar and alcohol.

6. Fermented food, if you can tolerate it, should be part of a gut recovery diet as it encourages the growth of good microbiota.
7. Probiotics are not necessary after fecal transplant and may upset the new flora.
8. Don't risk experimenting with a new diet after fecal transplant as it might unsettle your new flora. Stick to safe, known foods for at least 3 months then gradually introduce new foods.
9. Don't over-engineer it; leave Mother Nature alone to do her good work.

Who can be the donor?

Donor can be a family member or unrelated healthy person. To be an eligible donor, person must be at least 18 years old, in excellent health and on a healthy diet. His stool should look like a 2, 3 or 4 on the ***Bristol stool chart***. He should have ideal weight and excellent digestion history and he should not be on any medication. He should be sound in body and spirit and must satisfy the requirements of this ***Donor Screening Questionnaire***. Periodic health check of donors is mandatory after every 3 months.


Bristol Stool Chart
Type 1
Separate hard lumps, like nuts (hard to pass)
Type 2
Sausage-shaped but lumpy
Type 3
Like a sausage but with cracks on its surface
Type 4
Like a sausage or snake, smooth and soft
Type 5
Soft blobs with clear-cut edges (passed easily)
Type 6
Fluffy pieces with ragged edges, a mushy stool
Type 7
Watery, no solid pieces. Entirely Liquid

Pic 2 : Bristol stool chart

Your responsibilities as a Donor :

As a donor it is vitally important that you understand the instructions mentioned.

You need to make sufficient dietary and lifestyle changes for the duration of the patient's treatment to ensure that you will pass a bowel motion every day. For this, avoid food at risk of contamination and antibiotics. Also must commence a high fibre diet to improve quality of your flora. Donor should avoid junk food and should be on a balanced healthy diet. He should not be smoking or drinking alcohol. Donor should inform immediately about occurrence of any medical illness.

Where to use FMT?

Where standard medical therapy has failed to control the disease activity or patient develops frequent relapses requiring use of drugs like steroids which have side effects. Patients who do not tolerate or are allergic to standard therapies can be considered for FMT. It can also be used to maintain disease remission. It is a natural, medication free way to repopulate the intestinal microbiome.

How often FMT can be done ?

Different protocols have been worked out. Most of the patients require once a month session.

Is FMT safe?

To date, there have not been any documented cases of infection transmitted through FMT. However, stool is considered to be a bodily fluid, so the biggest immediate risk is contracting an illness from your donor. Testing of donor will eliminate most of the risks. According to few articles, transient adverse responses after FMT have been reported, including mild fever, abdominal pain, diarrhoea, exhaust, flatulence, and fatigue. However, these adverse effects are self-limiting.

Points to keep in mind After FMT :

- You will get into a routine with FMT. The first time is the hardest and like everything it gets easier with practice. Hopefully you won't have to do it for too long.
- Take liquid diet for one day after FMT
- Try and hold it in for at least 6 hours.
- A high fiber diet will help grow your new microbiota, but don't overdo it.

INFORMED PATIENT CONSENT

I.....D/o, W/o, S/o.....

..... am willing to participate in the study "**PATTERN OF RESPONSE TO FECAL MICROBIOTA TRANSPLANTATION IN PATIENTS WITH ACTIVE ULCERATIVE COLITIS**". The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

....

Signature of the Witness Signature of the patient

Name:

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____ निवासी _____ इस शोधकार्य **"PATTERN OF RESPONSE TO FECAL MICROBIOTA TRANSPLANTATION IN PATIENTS WITH ACTIVE ULCERATIVE COLITIS "** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ _____

ਮੈਂ _____ ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ _____ ਵਾਸੀ _____ ਇਸ ਖੋਜ "**PATTERN OF RESPONSE TO FECAL MICROBIOTA TRANSPLANTATION IN PATIENTS WITH ACTIVE ULCERATIVE COLITIS**" ਵਿੱਚ ਹਿੱਸਾ ਲੇਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈਂ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈਂ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ/ਚਾਹੁੰਦੀ ਹਾਂ ਕਿ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂੰ ਕਿਸੇ ਵੀ ਤਰ੍ਹਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀਂ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂਮ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂੰ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕਿ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂੰ ਇਸ ਖੋਜ ਵਿੱਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂੰ ਇਹ ਯਕੀਨ ਹੈ ਕਿ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂੰ ਇਸ ਖੋਜ ਕੰਮ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ-ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈਂ ਇਸ ਖੋਜ ਕੰਮ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇਂ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀਂ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ _____

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ _____